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Atherosclerosis prevention: the role of special diets and functional food

Vasily P. Karagodin[1], Vasily N. Sukhorukov[2,3], Alexander N. Orekhov[2,3], Shaw-Fang Yet[4], Igor A. Sobenin[2]

[1]Plekhanov Russian University of Economics, Stremyanny Pereulok 36, 117997 Moscow, Russia, [2]Institute of Human Morphology, Tsyurupa str. 3, 117418, Moscow, Russia, [3]Institute of General Pathology and Pathophysiology, Baltiyskaya str. 8, 125315 Moscow, Russia, [4] Institute of Cellular and System Medicine, National Health Research Institutes, 35 Keyan Road, Zhunan Town, Miaoli County 35053, Taiwan R.O.C., [5]Laboratory of Medical Genetics, National Medical Research Center of Cardiology, 15A 3-rd Cherepkovskaya Street, Moscow 121552, Russia

TABLE OF CONTENTS

1. ABSTRACT

Accumulating evidence highlight the importance of diet in the pathogenesis as well as prevention of atherosclerosis. In this review, we summarize the results of recent studies that demonstrate direct and indirect effects if functional foods and their analogues in prevention of initiation and progression of atherosclerosis. We discuss the epidemiological and clinical observations of such diets and dicuss their effects on the pathological mechanisms that drive atherosclerosis at cellular and molecular level.

2. INTRODUCTION

Diet is an important factor in the development of atherosclerosis which leads to hypercholesterolemia, ischemic heart disease and myocardial infarction. A high-calorie diet, with a great proportion of saturated fat and cholesterol, increases the risk of cardiovascular disease (CVD) (1-2). Diet is also responisble for the differences in the risk level and clinical manifestations of atherosclerosis among individuals in different populations (3-5). Thus, it follows that special diets can also be made that halt or slow down the atherogenesis.

Atherosclerosis results from accumulation of lipids, primarily free cholesterol, cholesterol esters, and low-density lipoprotein (LDL) in the vascular wall (7-9). However, chemical modification of the lipoprotein particles is necessary for acquiring atherogenic properties, since, in most cases, native LDL does not cause intracellular accumulation of lipid (10). Among the atherogenic modification of LDL, desialylation facilitates subsequent oxidation and formation of aggregated lipid in human plasma (12). Apart from alterations in blood lipid profile, inflammation is also considered as a key factor in the development of atherosclerosis (11).

A good strategy for preventing atherosclerosis is to prevent the development of modified LDL with atherogenic potential. For example, high-density lipoprotein (HDL) appear to have a protective role in atherogenesis (13). During the recent years, the development of

pharmacological approaches to treat atherosclerosis received much attention. However, the clinical application of the existing drugs is quite limited due to their narrow indications, side effects and relatively high cost. Lifestyle modification, including introduction of special diets, dietary supplements and functional foods (FF), appear to be promising alternatives to pharmacological intervention for prevention or treatment of atherosclerosis (14-15). Most diets and dietary supplements are characterized by affordable price and little or no known side effects, which allows their long-term, or even lifelong use. Here, we describe the diets with anti-atherogenic effects, mainly from plants, that prevent the occurrence and progression of atherosclerotic lesions and summarize the recent achievements in the development of functional foods and diets aimed at prevention and treatment of atherosclerosis (6).

3. NUTRITION AND ATHEROSCLEROSIS

The development of special diets targeting atherogenesis is complicated by the lack of a solid research algorithm. Tests based on cultured cells may be helpful for preliminary screening and rough assessment of the anti-atherogenic potential of different food components. Our group has developed a number of cell-based and *in vivo* tests for these purposes that characterized the cellular accumulation of cholesterol and efflux, expression of inflammatory cytokines (HLA-DR, ICAM-1, IL-1 and TNF-α), and changes in activity of sialidase in blood (16-17).

1. Aortic intima cell model for assessing cholesterol accumulation, cholesterol efflux and cytokine production
2. Cellular model based on human monocyte-derived macrophages to assess the accumulation and efflux of cholesterol
3. An enzymatic model for determining activity of sialidase and searching for agents that prevent atherogenic modification of LDL
4. In the *in vivo* model, the atherogenic factors are measured in the plasma of volunteers before and after consumption of distinct food substances.

In one model, the effect of eight different plants on monocyte-derived macrophages on removal of excess cholestrol was tested (17). Among these, onion (*Allium cepa*) powder likely, through flavonoids, saponins, allicin and ascorbic acid exerted anti-atherosclerotic effect including a decrease in cholesterol content in lipid-loaded cells (17). Using primary culture of intimal aortic cells, we identified a positive correlation between the accumulation of intracellular lipids and the expression of HLA-DR, TNF-α and IL-1 (17). These studies also revealed that *Allium cepa*, calendula (*Calendula officinalis*), violet (*Viola tricolor*) and black elder berries (*Sambucus nigra*) reduced inflammatory cytokines (17).

The anti-inflammatory efficacy of the combination of these plants was as high as 88% of that of diclofenac, one of the most potent non-steroid anti-inflammatory drugs. The active ingredients of plants that convey anti-inflammatory properties may include carotenoids, flavonoids, saponins, phytosterols, flavon glycoside violacvercetin and anthocyanin glycosides (delphinidin, peonidin, violin). Grape seed, hop, garlic and green tea also have exhibited anti-atherogenic potential(17).

One of the events associated with atherosclerosis is the formation of foam cells and recruitment of macrophages with a pro-inflammatory phenotype in the atheromas. A combination of three biologically active agents (phytosterols, omega-3 polyunsaturated fatty acids, and flavanols) inhibited the recruitment of monocytes, pro-inflammatory polarization of macrophages as well as formation of foam cells (18). Other effects included the increase of ApoA-I-mediated efflux of cholesterol from foam cells, which was independent from the presence of phytosterols in the tested mixture and suppression of the expression of two antiatherogenic genes.

3.1. Traditional foods and atherosclerosis

Among the traditional foods tomatoes, that are rich in lycopene, have a positive influence on body weight, blood pressure, blood glucose level, lipid metabolism, and endothelial function, and show antioxidant and anti-inflammatory properties (19-20). Moreover, the anti-atherosclerotic effect of tomatoes appears to depend on the method of their culinary processing (21). High levels of polyunsaturated fatty

acids (PUFA) in fish are thought to have anti-atherosclerotic properties. However, according to a report, intake of fatty fish or fish oil as a dietary supplement had no impact on the formation of atherosclerotic plaques visible on ultrasound examination of carotid arteries (22). Likely independent from PUFA, and by their specific contents of peptides and amino acids, including taurine and glycine, consumption of lean fish reduced the likelihood of developing plaques (22-24). Moreover, it has been shown that the beneficial activity of PUFA may decrease during thermal processing of fish (25- 26). Cranberry, has been shown to exert beneficial effect on inflammation, oxidative stress, blood pressure, endothelial function, regulation of blood glucose level, and a variety of biomarkers (27). These effects are largely conveyed mostly through polyphenols along with other substances including phenolic acids, isoprenoids, and oligosaccharides. Cornel (*Cornelian cherry*), likely through their polyphenol compounds, also has been reported to have anti-atherosclerotic activity, and to alter lipid-carbohydrate metabolism, platelet activity, total cholesterol, plasma LDL, and markers of inflammation and oxidative stress (28). Molecular and cellular effects of polyphenols, tocopherols and PUFAs persent in olive oil have been recently described (29). The most important molecular effect has been attributed to reduced oxidative stress that leads to endothelial dysfunction. It appears that components in olive oil attenuate oxidative stress and improve the endothelial function through their anti-inflammatory, anti-oxidant, and anti-thrombotic properties (30).

3.2. Functional food and biologically active food supplements

The concept of “functional food” has been evolving since the early 1980s, and the definition of the relevant product categories has undergone repeated changes. One of the latest definitions of functional food (FF) is natural or processed foods that contain known or unknown biologically-active compounds; which provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic diseases (31). Thus, FF can be either natural or processed, that is, specially designed, such as folate-fortified cereal or vitamin C-enriched milk. Moreover, in some countries, the definition of FF also includes dietary supplements in the form of pills and capsules. Methods for production of designed FF have been described in detail elsewhere (32). Regarding the effects of nutritionally engineered foods on atherosclerosis, only a limited number of studies exist (33-34). Among these, feeding animals FF consisting of chicken egg yolk conjugated with linoleic acid led to reduction of blood cholesterol, and anti-inflammatory and modified the composition of cholesterol-containing plaques (35). Extracts of leaves of *Mallotus furetianus* fed to rats for nine weeks, modified lipid profile of blood associated with changes in histology and and the thickness of the intima-media (36). A 2-year study using a FF form of garlic (Allicor) and a series of double-blind placebo-controlled clinical trials using this formulation have established the anti-atherosclerotic and preventative effects of Allicor in reducing the risk of developing atheroscloerosis as well as a direct effect at the level of the vascular wall (37). Other dietary supplements with similar composition that have shown to inhibit accumulation of lipid in the vascular wall are Inflaminat and Karinat (38).

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Abbreviations: FF: functional food, CVD: cardiovascular disease, LDL: low-density lipoproteins, HDL: high-density lipoproteins, PUFAs: omega-3 polyunsaturated fatty acids

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Send correspondence to: Vasily Karagodin, Plekhanov Russian University of Economics, Stremyanny Pereulok, 36, 117997 Moscow, Russia, Tel: 74956053551, E-mail: vpka@mail.ru