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Prevention of atherosclerosis: the role of special diets and functional foods

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1. ABSTRACT

The importance of diet for prevention of atherosclerosis is supported by numerous studies. However, to date, no rigorous method exists to assess its impact. Dietary ingredients and supplements and functional foods receive special attention as promising components in prevention of atherosclerosis. In this review, we summarize the results of recent studies that demonstrate the direct and indirect effects of functional foods and dietary components on the initiation and progression of atherosclerosis. We discuss the possible effects of different diets on the pathological mechanisms at cellular and molecular level, as well as epidemiological and clinical observations.

2. INTRODUCTION

Unhealthy eating habits have long been known as one of the important risk factors in the development of atherosclerosis. As a disease-modifying factor, diet accounts for the differences in the risk level and clinical manifestations of atherosclerosis in different populations. Many observations were made regarding the association of a high-calorie diet, which contains a great proportion of saturated fat and cholesterol, and the increased risk of cardiovascular disease (CVD) (1). Tight links have been revealed between clinical consequences of atherosclerosis, such as ischemic heart disease or myocardial infarction, and diet-related risk factors, such as arterial hypertension, obesity, diabetes mellitus and hypercholesterolemia. Establishing this connection allowed for the development of numerous guidelines and diet recommendations that take into account the amounts of vitamins, carbohydrates, unsaturated fatty acids, antioxidants, minerals and a number of other biologically active substances in dietary products (2). However, despite the great number of publications, causal relationship between diet and the development of atherosclerosis remains has not been clearly established. Studying dose-dependent effects of food is challenging because of the complexity of food composition and poor standardization of the contents of active ingredients, and because short-term intake of a certain food has little effect on specific pathological process that is being examined. The duration of consumption of nutrients is also of crucial importance for assessing the impact of certain diets on atherosclerosis. Another important problem of studies that examine the effect of diet on disease is finding the appropriate control population for comparative analysis. Therefore, our knowledge on how food impacts atherogenesis, as well as of pharmacokinetics of different active ingredients present in foods, remains limited (3).

One of the challenges in interpreting the results of anti-atherosclerotic effects of foods is shifting the focus from the effects of food on risk factors, such as hypertension, diabetes, or blood cholesterol level, to the direct effect of food on atherogenesis (4-5). In the first part of this review, we describe the concept of direct anti-atherosclerotic effects of dietary components and, the observations made, using cellular models of the disease. In the second part of the review, we summarize recent achievements in the development of functional foods (FF) and diets aimed at prevention and treatment of atherosclerosis.

3. MODELLING ATHEROSCLEROSIS PATHOGENESIS AND PROGRESSION

Direct effect of anti-atherosclerosis interventions can be defined as preventing the occurrence and progression of atherosclerotic lesions in the affected arterial wall and, ideally, inducing the regression of existing lesions (6). Currently, no known medication has such direct anti-atherosclerotic effect. A typical feature of atherosclerosis is accumulation of lipids, primarily free cholesterol and cholesterol esters, in the vascular wall (7, 8). Low-density lipoprotein (LDL) is the main source of accumulating lipids (9). However, not all forms of LDL are equally important in atherogenesis. In experimental conditions, treatment with native LDL did not lead to intracellular lipid accumulation in the cells and macrophages that reside in the arterial wall. Further analysis showed that the chemical modification of lipoprotein particles, such as desialylation or oxidation, is a necessary step for modification of lipoprotein to acquire atherogenic properties (10). Direct treatment of atherosclerosis should include prevention of the formation of atherogenic modified LDL and its accumulation in the vascular wall.

Apart from alterations of blood lipid profile, there are other factors such as inflammation are equally important for atherogenesisand atherosclerosis is currently being regarded as a chronic inflammatory condition (11). Among the atherogenic LDL modifications, desialylation is likely to be the key change, since it facilitates subsequent oxidation and self-association of LDL particles and can be observed in human blood plasma (12). While elevated LDL is a known risk factor for atherosclerosis, high-density lipoproteins (HDL) appear to have a protective role in reducing the development of atherosclerotic lesions (13).

During the recent years, development of pharmacological approaches to treat atherosclerosis has also received much attention. However, clinical application of existing anti-atherosclerotic drugs is limited due to narrow indications, associated side effects and their relatively high cost. Lifestyle modifications, and introduction of special diets, dietary supplements and FF, appear to be a promising alternative to the pharmacological treatment. Most diets and dietary supplements are characterized by an affordable price and little or no known side effects, which allows their long-term, or even lifelong use. At the same time, diets may prove effective for prevention and alleviation of atherosclerosis (14-15).

Development of special anti-atherosclerosis diets is complicated by the lack of a solid research approach. Tests based on cultured cells may be helpful for preliminary screening and rough assessment of anti-atherogenic potential of different food components. Our group has developed a number of cell-based tests (16-17). These models include:

1. Aortic intima cell model. This model is used for assessing cholesterol accumulation, cholesterol efflux and cytokine production;

2. Cellular model. This model is used based on human monocyte-derived macrophages to assess the accumulation and efflux of cholesterol;

3. Enzymatic model. This model is used for determining sialidase activity and searching for agents that prevent atherogenic modification of LDL.

A series of *in vitro* and *ex vivo* experiments using these models aimed to investigate the influence of different food components on the following processes:

1. Cellular cholesterol accumulation and efflux
2. Expression of inflammatory cytokines (HLA-DR, ICAM-1, IL-1 and TNF-α)
3. Changes of blood sialidase activity

This work resulted in identification of anti-atherosclerotic and atherogenic effects of different medicinal plants and food components. The *ex vivo* model has allowed measuring atherogenic factors in the blood plasma of volunteers who consumed the tested foods. In particular, evaluation of the effects of 14 plants in these experiments revealed that consumption of licorice root prevented atherogenic modification of LDL (17). The possible components of licorice that may convey this effect are flavonoids and triterpenic saponins.

Cellular model based on monocyte-derived macrophages was used to study the effect of 8 dietary and medicinal plants on the removal of excess cholesterol from the vascular wall. Onion (*Allium cepa*) powder was shown to be a very effective anti-atherosclerotic component that promoted decreasing of cholesterol content in lipid-loaded cells (17). The effect of onion is considered to be due to the biological activity of flavonoids, saponins, allicin and ascorbic acid present in onion. Macrophages are capable of sensing lipids through liver X receptors (LXRs), oxysterol-activated nuclear receptors, and peroxisome proliferator-activated receptors (PPARs) that can respond to oxidized fatty acids and their derivatives. Ligands of LXRs and PPARs have pronounced protective effects against atherosclerosis through inhibition of the inflammatory response and intracellular lipid accumulation in the arterial wall (18). Some of the well-known components of edible plants, such as dehydroabietic acid (18-20) or methyl oleanonate (21) can have anti-inflammatory and anti-atherosclerotic effects through interaction with PPAR lipid sensor (22). Capsaicin, the pungent component of chili pepper, was demonstrated to have pronounced anti-inflammatory effect when applied to cultured macrophages (23). Moreover, capsaicin inhibited macrophage migration and release of pro-inflammatory cytokine. Another example of food-derived biologically active agent with potential anti-atherosclerosis properties is auraptene, a monoterpene contained in the peel of citrus fruits, which was identified as a PPAR agonist (24, 25).

A positive correlation between the accumulation of intracellular lipids and the expression of inflammatory molecules including HLA-DR, TNF-α and IL-1 was established in the experiments conducted on primary cultures of intimal aortic cells. These experiments revealed the anti-cytokine (anti-inflammatory) properties of different foods (17). Likewise, *in vitro* and *ex vivo* models were used for studying the potential anti-inflammatory activity of 31 plants. As a result, several medicinal plants were identified as especially promising for prevention of atherosclerosis, including calendula (*Calendula officinalis*), violet (*Viola tricolor*) and black elder berries (*Sambucus nigra*) (17). The anti-inflammatory effect achieved by 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 these plants that convey anti-inflammatory properties may include carotenoids, flavonoids, saponins, phytosterols, flavon glycoside violacvercetin and anthocyanin glycosides (delphinidin, peonidin, violin). In addition to the above listed plants, most of which are used as dietary components, inhibition of atherogenesis was has also been demonstrated for grape seed, hop, garlic and green tea (17). Therefore, enzymatic and cellular models that allow mimicking the key processes of atherogenesis were useful for identifying food components that potentially have direct anti-atherosclerotic effects. It is possible that similar methodological approach can be used to detect the effects of food substances with a more complex composition.

4. NUTRITION AND ATHEROSCLEROSIS

The relationship between food intake and atherosclerosis has been explored in numerous studies with different designs. These studies considered the effects of both whole foods (processed and unprocessed) and their individual ingredients, as well as dietary supplements, functional nutritional products and various therapeutic and prophylactic diets. In most studies, molecular and cellular mechanisms of biological activity of food components remained beyond the research scope. Instead, the authors focused on the impact of different foods on known risk factors and metabolic status of study subjects.

4.1. Studies in cell models of atherosclerosis

In a recent study, anti-atherosclerotic effects of biologically active agents were evaluated using a cell model based on macrophages, an approach that is methodologically similar to that of the *in vitro* models described above (26). A combination of three biologically active agents (phytosterols, omega-3 polyunsaturated fatty acids, and flavanols) inhibited the formation of foam cells, monocyte recruitment and pro-inflammatory polarization of macrophages. The observed effects included potential anti-atherosclerotic activity relevant to the different stages of the disease (Author: Place reference). In particular, pro-inflammatory polarization of macrophages is known to be associated with atherosclerosis. Suppression of this process may have a therapeutic value for prevention and treatment of atherosclerosis . Other effects of the herbal preparation has 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 anti-atherogenic genes (Author: Place reference). The authors highlighted the absence of antagonistic or synergistic interactions between the individual components of the formulation and concluded that further research of this mixture, including experiments on an *in vivo* model, is required to show the clinical usefullness of the findings.

The abovementioned phytosterols that promote the reduction of blood serum LDL were also found promising for prevention of atherogenesis (27). For instance, it was demonstrated that these inhibit the inflammatory processes. Experiments on macrophages demonstrated that desmosterol, an intermediate product in cholesterol synthesis, could reduce lipid accumulation and inflammatory response in cultured cells through regulation of inflammatory genes (28). Sitosterol and campesterol were also shown to influence the production of inflammatory factors by macrophages (29-31). Phytosterols exert anti-inflammatory effects not only on macrophages, but also in T-lymphocytes (32).

4.2. Traditional foods and atherosclerosis

Among the traditional foods, several components were shown to have anti-atherosclerotic effects (Table 1). Tomatoes, that are rich in lycopene, are often mentioned among the healthy food categories. The protective effect of lycopene was demonstrated to be dose-dependent (33). Data from clinical studies that assess the beneficial effects of tomatoes and tomato products on body weight, blood pressure, blood glucose level, lipid metabolism, and endothelial function, as well as their antioxidant and anti-inflammatory properties, have been discussed in a recent review (34). However, several studies failed to confirm the antiplatelet effect of tomatoes. Moreover, the anti-atherosclerotic effects of tomatoes appear to depend on the culinary method of their processing (35), and the usefulness of tomato-based diet remains to be demonstrated.

Fish, which contains high levels of polyunsaturated fatty acids (PUFA) with potential anti-atherosclerotic properties. However, the original population-based study conducted over a period of 7 years did not support the hypothesis that high consumption of fish is beneficial for prevention of atherosclerosis (36). Intake of fatty fish or fish oil dietary supplements had no impact on the formation of atherosclerotic plaques visible on ultrasound

Table 1. Common dietary components that have potential anti-atherosclerosis activity

Dietary component	Effects	Possible active ingredient	Reference
Tomatoes	Antioxidant Alleviate endothelial dysfunction Anti-inflammatory Normalization of blood pressure, blood glucose and lipids levels and metabolism	Lycopene	(33, 34)
Fish and seafood	No proven anti-atherosclerotic effect, but may be beneficial for atherosclerosis prevention	PUFA and other unknown components	(37, 38)
Cranberry	Antioxidant Alleviate endothelial dysfunction Anti-inflammatory Normalization of blood pressure and glucose level	Polyphenols, isoprenoids and other components	(41)
Cornel	Antioxidant Anti-inflammatory Antiplatelet Normalization of lipid-carbohydrate metabolism	Polyphenols	(42)
Olive oil	Antioxidant Alleviate endothelial dysfunction Anti-inflammatory Antithrombotic	Polyphenols, tocopherols and PUFA	(43)
PUFA, polyunsaturated fatty acids			

examination of carotid arteries. At the same time, consumption of lean fish reduced the likelihood of plaque development, which, according to the authors, indicates the existence of anti-atherosclerotic mechanisms independent from PUFA. These may be attributed to other components of fish, such as peptides and amino acids, including taurine and glycine (37, 38). In addition, the beneficial activity of PUFA may decrease during thermal processing of fish (39, 40).

One recent study has evaluated the potential anti-atherosclerotic effects of another dietary product, cranberry (41). In particular, the effects of cranberry on cellular (cardiometabolic) processes associated with atherosclerosis, were assessed. The authors evaluated the effect of cranberry consumption on the inflammatory and oxidative stress, blood pressure, endothelial function, regulation of blood glucose level, and a variety of biomarkers. The observed effects, were attributed mostly, to polyphenols that are present in berries. The observations were confirmed by a series of *in vitro* experiments, as well as in animal models. Moreover, the involvement of gut microbiota in the described effects was considered. The results pointed to the existence of certain synergy of polyphenols with cranberry phenolic acids, isoprenoids, oligosaccharides, and some other compounds. The proper interpretation of the obtained results was hindered by the differences in the marketed forms of cranberry products (juices, extracts or dried berries), the differences in doses used and the characteristics of the populations that were included in such studies.

Another recently published study described the anti-atherosclerotic activity of cornel (Cornelian cherry) (42). In this case, polyphenols were again considered as the possible active ingredients that convey the effect. The work revealed a pronounced effect of cornel on lipid-carbohydrate metabolism, platelet activity, total cholesterol, plasma LDL, and markers of inflammation and oxidative stress, as compared to statins. However, proper evaluation of the effects was hindered by the lack of standardization of dosages and duration of the food intake.

Molecular and cellular effects of polyphenols, tocopherols and PUFAs contained in olive oil have been described in a recent review (43).

The most important effect attributeed to this dietary product appears to be the prevention of the oxidative stress-induced endothelial dysfunction. It appeared that olive oil components have a potent capability of attenuating oxidative stress and improving the endothelial function through their anti-inflammatory, antioxidant, and anti-thrombotic properties. These effects, in turn, can reduce the risk and alleviate the progression of atherosclerosis. However, the authors also pointed out that oxidative stress could not be considered as the principal cause of atherosclerosis (44).

4.3. Functional food and biologically active food supplements

The concept of "functional food" has been evolving since early 1980s, and the definition of the relevant product categories has undergone repeated changes. One of the latest definitions of functional food (FF) is "functional food" as natural or processed. foods that contains known or unknown biologically-active compounds; the foods, in. defined, effective, and non-toxic amounts, provide a clinically proven and documented health benefit for the prevention, management, or treatment of a chronic disease" (45). Thus, FF can be either natural or processed, that is, specially designed, such as a 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 of designed FF production have been described in detail elsewhere (46).

Interestingly, the effects of nutritionally engineered foods on atherosclerosis appear to be less studied that those of natural foods (47). A recent review has questioned the feasibility of introducing phytosterols in the composition of dietary products to combat hypercholesterinoma, which is confirmed not only by animal studies, but also in clinical trials (48). Moreover, it was reported that studies in humans have failed to demonstrate the link between the consumption of phytosterol-enriched FF and vessel function (49). It has been suggested that consumption of polyphenol-containing FFs can be beneficial for patients with a high blood cholesterol level but who are at low risk for cardiovascular complications that do not need pharmacotherapy. FF can also be used as a supplement to pharmacotherapy in patients that have increased risk of atherosclerosis. Consumption of chicken egg yolk conjugated with linoleic acid by laboratory animals led to reduction of blood cholesterol and had anti-inflammatory and anti-atherogenic effects. As a result, this FF had beneficial effects on the composition of cholesterol-containing plaques (50). Extracts of *Mallotus furetianus* leaves consumed by rats for a period of 9 week showed a similar effect on blood lipid profile, histological features and the thickness of the intima-media s (51).

Various dietary supplements are often considered as FFs and used to achieve certain beneficial effects on health. However, relatively little experimental data are available on the effects of dietary supplements on atherosclerosis. One of the most detailed studies of anti-atherosclerotic effects of FFs has been provided for the garlic-based dietary supplement, registered under the name of Allicor (52). It has been suggested that that this FF exerts direct effect at the level of the vascular wall as well as indirect effects on atherosclerosis risk factors. . A 2-year study (The Atherosclerosis Monitoring and Atherogenic Reduction Study) and a series of double-blind placebo-controlled clinical trials have shown reliable clinical efficacy of Allikor for prevention of atherosclerosis. Other dietary supplements with similar composition including Inflaminat and Karinat have shownto inhibit lipid accumulation in the vascular wall (53).

4.4. Anti-atherosclerotic diets

The effects of special diets on atherosclerosis have been known for a long time (54). Studies evaluating the impact of different diets on cardiovascular risk factors usually focus on the contents of individual dietary components. However, the mechanisms of action of food components remain largely unclear, although it is often suggested that these mechanisms involve anti-inflammatory effects of biological substances, such as antioxidants and polyphenols. For example, the Mediterranean diet has been documents by clinical trials (55, 56). Nevertheless, it remains unclear whether this diet can have protective role in all human populations (57).

Dietary Approaches to Stop Hypertension is a diet that has been developed to reduce one of the risk factors of atherosclerosis (58). In addition, the diet reduced total cholesterol and LDL levels, homocysteine and inflammatory markers (59-61). Other cardioprotective diets include Portfolio Diet (62), Vegetarian Diet and Okinawa Diet (63). Their indirect effects on atherogenesis is associated with a decrease in the blood level of C-reactive protein (an inflammatory marker) (64) and cholesterol, as well as decrease of blood pressure and reduction of obesity (62).

5. CONCLUSIONS

The effects of nutritional factors on cardiovascular diseases, including atherosclerosis, have attracted much attention during the last 50 years. Some dietary components, such as plant products, fish, or seafoods appear to be promising. In particular, the Mediterranean diet has shown good results in controlled settings. However, most of the data available so far are related to reducing the risk factors of atherosclerosis, but not to directly inhibit cellular processes of atherogenesis. The development of cellular models have facilitated screening of food components for their beneficial properties, such as an anti-inflammatory activity. However, many questions remain open about the mechanisms of the observed effects and their dependence on the dose and duration of exposure.

6. ACKNOWLEDGEMENT

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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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