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Effect of carrageenan food supplement on patients with cardiovascular disease results in normalization of lipid profile and moderate modulation of immunity system markers

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ABSTRACT

The present study determines the effects of a short-term carrageenan supplement on the immune status and lipid profile in patients with ischemic heart disease. The immunomodulatory and hypocholesterolaemic effects of a carrageenan food supplement were investigated in 40 hypercholesterolaemic patients with cardiovascular heart disease who were randomly assigned to control and experimental groups, and 20 apparently healthy subjects who were assigned to the normal group. Supplementation with carrageenans did not induce hyperactivation of the immune system. Carrageenans moderately modulated all of the immunity system markers and caused statistically significant decreases in the following biomarkers of chronic inflammation: leucocytes by 15.9%, fibrinogen by 8.62%, and C-reactive protein by 13.03%. Supplementation with carrageenans significantly decreased cholesterol levels by 16.5% and low density lipoprotein cholesterol by 33.5%. In the group of patients under traditional treatment, the amount of total cholesterol and low density lipoprotein cholesterol decreased insignificantly by 6.2% and 10.7%, respectively. The atherosclerotic index, which was rather high in the control group, decreased significantly by 36.6% after the addition of the carrageenan food supplement.

1. Introduction

Our diet is known to be a risk factor for disorders ranging from cardiovascular disease to cancer, and evidence of the influence of dietary choices on the development of immune disorders is continually emerging [1]. The varied microflora housed in the large intestine is markedly affected by dietary fibres, the influence of which can also affect innate immune responses of the gut mucosa both directly and indirectly [2]. For example, the effects of different types of dietary fibres on the intestinal mucus barrier have previously been assessed in a range of animal models. Fibres and fibre sources, such as alginates, ispaghula husk, wheat bran, ulvan and carrageenan seem to increase the protective potential of the colonic mucus barrier compared with diets rich in cellulose, pectin or gum arabic [2,3]. Another interesting property among the wide range of claimed beneficial effects of dietary fibres is their ability to lower cholesterol, although the mechanisms underlying the hypocholesterolaemic effect of dietary fibre remain undefined.

A deficiency of food fibres in the human diet contributes to gastrointestinal, metabolic and cardiovascular disease [4]. Food fibres are able to reduce the risk of developing cardiovascular disorders by means of improving lipid indices, leading to increased insulin sensitivity and fibrinolytic activity [5–7]. The term dietary fibre is attributed to carbohydrates of plant origin that are indigestible by human enzymes and encompasses a range of divergent compounds that differentially affect numerous important gastrointestinal and systemic bodily processes. Although it can be provided by a supplement, except in certain therapeutic situations, dietary fibre should be obtained through the consumption of natural sources, such as cereals, fruits, vegetables or legumes [8]. Food supplements support an organism within physiological limits, i.e., they act as supportive substances in a complex therapy [9].

One source of food fibre is various seaweeds. There have been a great deal of investigations in animal models that have studied the hypocholesterolaemic effects of various edible seaweeds, such as *Bladder wrack*, Nori, Porphyran, *Ecklonia stolonifera*, *Solieria robusta*, *Lyengaria*, *Eucheuma cottonii, Sargassum polycystum, Caulerpa lentilliferra*, *Fucus vesiculosus*, *Wakame* and *Caulerpa racemosa* [10].

The polysaccharides from marine algae, carrageenans, are considered an additional source of food fibre because of their unique physicochemical properties and structural diversity, which cause a wide range of physiological effects. Carrageenans are widely used as powerful gelling and stabilising agents, which is permitted under the regulations of the International Food Additive and Drug Committee, the Food and Agriculture Organization and the World Health

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Organization [11,12]. Due to the vast use of carrageenan as a food component, intensive research of its physiological activity has been carried out in recent years [13]. Carrageenans exhibit a wide range of biological properties, including, immune modulation and anticancer and antivirus properties, etc. [14–16]. Moreover, previous studies have shown that carrageenan, when used as a component of Filipino dishes, has hypoglycaemic effects in apparently healthy people [17]. An analysis of lipid profiles in volunteers regularly receiving dietary carrageenan showed significant decreases in blood cholesterol and lipid levels [17].

The present clinical trial was designed to investigate the effects of a carrageenan food supplement on the immunity status and lipid profile in patients with cardiovascular disease.

2. Materials and methods

The biologically active food supplement "Carrageenan-DV"® (Pacific Institute of Bioorganic Chemistry, Far East Branch of the Russian Academy of Sciences, Vladivostok, Russian Federation) is composed of two structural types of carrageenans (κ and λ in the ratio 3:1) and is isolated from the Far-East red alga *Chondrus armatus* (Gigartinaceae). The supplement meets the requirements for food supplements and is recommended as an additional source of food fibre.

Patients diagnosed with ischemic heart disease (IHD) and healthy volunteers were selected for the current clinical trial based on an analysis of out-patient medical records obtained from the Medical Association of the Far East Branch of the Russian Academy of Sciences. After the patients were selected, they were enrolled in the current clinical trial to test the effects of the carrageenan food supplement.

The selection criteria for patients that were included in the control group were as follows:

1 confirmed diagnosis of IHD;
2 presence of angina of effort (functional class II–III), isolated or in combination with arterial hypertension;
3 age 44–64;
4 opposition to long-term background treatment;
5 presence of clinical and laboratory results for a period of 30–40 days (complete blood count, lipid profile, immunity status, fibrinogen, C-reactive protein).

The selection criteria for patients that were included in the experimental group were as follows:

1 must fulfill all of the criteria of the control group;
2 had taken a carrageenan food supplement.

Patients were excluded from the study based on the following criteria:

1 presence of decompensated comorbidities;
2 presence of lab values indicating serious dysfunctions of a number of organs and systems (liver, kidney, blood).

Formation of the experimental and control groups followed a randomised design (method of random selection) taking into account age and common status of the patients.

To assess the efficacy of carrageenan fibre supplementation, we assessed various parameters in 60 patients who were divided into three groups: apparently healthy subjects (normal group; $n = 20$), IHD patients opposed to background treatment (control group; $n = 20$), and IHD patients opposed to background treatment and provided carrageenans (experimental group; $n = 20$). The patients in the experimental group were given a 250 mg capsule containing a food supplement, based on carrageenans, each day for 20 days. The lipid profile and the immune status of the control group were analysed at baseline (BEFORE) and 30–40 days post-baseline (AFTER), while the lipid profile and immune status of the experimental group were analysed at baseline (BEFORE) and following 14–21 days of food supplement administration (AFTER).

The placebo effect was not relevant to the current trial because of two reasons: the patients in the both groups (control and experimental) were opposed to background therapy, and on an ethical basis. The World Medical Association suggests, "extreme care must be taken to avoid abuse of this option" [18]. In addition, valid ways to estimate the size of placebo effects in daily patient care have yet to be developed [19]. Placebo effects have been reported to improve outcomes in patients with cardiovascular diseases [20]; therefore, the conclusions from our data should be considered given this limitation.

The following lab parameters were selected from out-patient medical records to achieve the goals of this study:

1 Immunophenotyping of lymphocytes was conducted using monoclonal antibodies specific for the D3, CD4, CD8, CD22, CD16, CD25, CD95 antigens (Vitebsk, Belarus).
2 Serum immunoglobulin (IgG, M, A) content was assessed using one-dimensional radial immunodiffusion in an agar gel [21].
3 Neutrophil activity from peripheral blood was measured by the unified method [21]: phagocytic index (PI) – percent of neutrophils participating in phagocytosis; phagocytic number (PN) – the average number of microbe cells per phagocytic neutrophil; phagocytosis completeness (PC) – the killing ability of neutrophils.
4 Total serum cholesterol (TC), triglycerides, and high-density-lipoprotein cholesterol (HDL-C) concentrations were measured using test systems obtained from "Biocon," "Human" (Germany), "DiaSys" (Germany), "Vector-Best" (Russia), in a biochemical analyser Analette, "Anti" (USA). Low-density-lipoprotein cholesterol (LDL-C) was measured according to the Medical Association protocol. The atherosclerotic index (AI) was calculated as (TC-HDL-C)/HDL-C.
5 The level of C-reactive protein was determined by test-kits based on the ELISA method (Vektor-Best, Russia).
6 The amount of fibrinogen in plasma was measured by a method described elsewhere [22].
7 Body mass index is expressed as the body weight in kilograms divided by the height squared in metres.

2.1. Statistical analysis

The parameters obtained in the study are presented as the mean values ± SEM. Statistical analyses of clinical data were performed using the Statistica 6 application packet. To confirm the normal distribution of the data, the distribution of variables was investigated using the Shapiro-Wilks test. When this criterion was fulfilled, further analysis was carried out by means of paired *t*-tests. The significance level was set at $P < 0.05$.

3. Results and discussion

A growing body of literature suggests that inflammation is pivotal in all phases of atherosclerosis, and biomarkers of inflammation, especially high sensitivity C-reactive protein (CRP), have been shown in various studies to predict cardiovascular events [23]. Based on these data, the effect of supplementation with carrageenan fibres on the immune status of human subjects with IHD opposed to long-term maintenance therapy was studied.

Baseline (BEFORE) parameters in the IHD patients opposed to long-term maintenance therapy (control and experimental groups) did not show disturbances in the phenotypic and functional activity of peripheral blood lymphocytes, although some significant differences in immune status parameters compared with the normal group remained within normal limits. The difference in the immunity status was considered significant if the value was abnormal or changed more