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The effect of cardioprotective diet rich with natural antioxidants on chronic inflammation and oxidized LDL during cardiac rehabilitation in patients after acute myocardial infarction

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ABSTRACT

Background: Chronic inflammation, the fundamental pathogenetic process of atherosclerosis, can be modified by pharmacological and non-pharmacological measures as a part of secondary prevention after acute myocardial infarction (AMI). The aim of our study was to determine the effect of diet, rich with natural antioxidants, added to physical activity (as a part of cardiac rehabilitation (CR) program) on inflammatory markers and ox-LDL, a marker of oxidative stress, closely involved in the process of chronic inflammation.
Methods: 41 male patients after AMI undergoing CR were divided into a diet group (supervised cardioprotective diet throughout the CR), and control group (CR without diet). We measured hsCRP, leucocytes, neutrophils, IL-6, oxLDL, exercise capacity and classic risk factors before and after CR program.
Results: Patients from the diet group presented with a significant decline in classic risk factors (BMI, waist circumference, waist to hip ratio, systolic blood pressure, heart rate, blood glucose, total cholesterol, LDL, TAG) and inflammatory markers (hsCRP, leucocytes, neutrophils) compared to control group. Furthermore, when studying nonsmokers, we observed significant decline of oxLDL in the diet group.
Conclusions: The addition of cardioprotective diet, rich with natural antioxidants, to physical activity as a part of a CR program, positively modifies not just classic risk factors and exercise capacity, but also diminishes chronic inflammation markers. These effects, and oxLDL decline were most prominent in nonsmoking patients.

1. Background

Acute myocardial infarction (AMI) is a common manifestation of atherosclerotic coronary artery disease (CAD), which is one of the most important causes of mortality in the developed world [1,2]. Although improved management has significantly lowered CAD mortality [3], we are constantly searching for new strategies to influence the cardinal pathological process of atherosclerosis; to diminish inflammation [4]. On the contrary, oxidized low density lipoprotein (oxLDL), a useful marker of coronary artery disease [5], exhibits a marked influence on chronic inflammation, since it stimulates the release of chemotactic factors, cytokines and growth factors from artery wall cells, which play an important role in the development and progression of atherosclerotic plaque [6]. Furthermore, it was shown in vivo that host response to infection and inflammation itself induces LDL oxidation [7], so not only oxLDL stimulates inflammation but also the opposite happens. This confirms the existence of a strong connection between inflammatory response and oxLDL.

Regarding pharmacological therapy, statins and acetylsalicylic acid have already been proven to effectively reduce low-grade inflammation in AMI survivors [8–10] and also to protect LDL against oxidation [11,12]. Non-pharmacological measures such as physical activity and diet are also gaining recognition as non-classic risk factor modifiers. Physical activity is associated with diminished inflammation in adults with or without CAD, independently of

Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; CR, cardiac rehabilitation; LDL, low density lipoprotein; HDL, high density lipoprotein; TAG, triglycerides; hsCRP, high sensitivity CRP; oxLDL, oxidized LDL; IL-6, interleukin 6; BMI, body mass index; BP, blood pressure

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body composition and weight loss [13,14]. Furthermore, cardioprotective diet also improves survival in patients after AMI [15,16]. In addition, it has been shown that diet can also reduce the degree of inflammatory markers such as hsCRP and IL-6, not only in patients with developed coronary heart disease [17], but also in healthy adults at high risk for developing CAD [18]. Whereas many research works have proven favorable effects of coupled diet and physical exercise on inflammation in adults with high risk for CAD [19,20], we did not find any studies describing the effects of cardioprotective diet added to exercise training in patients after acute AMI (fully developed CAD).

The aim of our study was to explore how the addition of a cardioprotective diet (rich with natural antioxidants) to physical activity, which is as an integral part of a rehabilitation program, influences not just exercise capacity and classic risk factors for CAD, but also inflammatory markers including high sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6) and oxLDL. The secondary aim of the study was introduced subsequently since the results were less pronounced as we expected at the commencement of the study. In search of confounding factors that could influence inflammation and oxidation markers we further divided the patients into smoker and nonsmoker groups.

2. Materials and methods

2.1. Patients

Forty-one male patients with the median age of 59 years (minimum 36 years, maximum 73 years), discharged from the hospital at least 2 and not more than 9 weeks after AMI were included in our study.

Patients were successively recruited from the standard short-term (two-week) cardiac rehabilitation (CR) program. In Slovenia the national insurance company funds such CR programs for all patients after AMI. Their aims are to improve patients' physical performance and educate them about prevention of further disease progression, emphasizing the importance of drug therapy and lifestyle changes. The exercise program is supervised and all patients participate in lectures about healthy, cardioprotective diet, however they are allowed to choose their meals by themselves.

All patients after AMI were optimally treated according to current guidelines [2]. All patients were receiving acetylsalicylic acid 100 mg daily (combined with clopidogrel in 9 patients, prasugrel in 18 or ticagrelor in 13 patients for a year after AMI), angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers and statins. All patients were treated with appropriate statin doses (31 of them were receiving rosuvastatin, 9 atorvastatin and one simvastatin), so that the target values recommended by ECS were met. All but three patients were taking beta-blockers and one patient was on ivabradine. The patient group consisted of 21 smokers and 20 nonsmokers. We defined nonsmokers as patients who never smoked or stopped smoking at least a year before AMI occurred (most of them had quit smoking many years before AMI occurred).

After we acquired informed consent each patient was sorted to either a diet (21 patients, 10 nonsmokers and 11 smokers) or a control group of patients (20 patients, 10 nonsmokers and 10 smokers). The patients from the diet group consumed cardioprotective diet rich with natural antioxidants throughout the CR, individually prepared by a clinical dietitian (explained in detail in the chapter Diet). All patients were advised to immediately report to us about possible side effects of the diet, and all the patients had the right to cease from the study at any time due personal or other reasons (such as allergic reactions and changes in digestion).

To minimize the influence of smoking and statin treatment on the effects of diet intervention during CR, we sorted out the patients to the diet or the control group according to smoking status and treatment with statins. In that way, we obtained groups which did not differ in percentage of smokers ($p = 0.78$) and were also balanced regarding statin doses (no statistically significant differences were seen in equivalent statin doses between diets and controls, $p = 0.380$). Patients from the diet group proved to be significantly younger than patients included in the control group (52 vs 62.5 years, $p = 0.013$), what can be explained by higher motivation of younger patients, who agreed to participate in the intervention group.

Exclusion criteria for the studied group were: female gender, symptoms, signs and laboratory indications of acute infection, known diseases with ongoing chronic inflammation, and daily intake of dietary supplements and/or vitamins, AMI treated with urgent coronary bypass surgery, complications of AMI involving the need for urgent surgical intervention and other larger surgical procedures needed during hospitalization in the coronary unit.

The study was approved by the Slovenian Board for Medical Ethics No. 159/06/10 and all subjects gave their written informed consent.

2.2. Study design

2.2.1. CR protocol

The CR program was carried out in a local health resort. The rehabilitation comprised a fourteen-day long, gradual training regimen in accordance with the Position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Rehabilitation and Prevention [21]. The program consisted of supervised physical activity, which included daily interval ergometric training (25–30 min), during which we gradually increased the load with intervals of low intensity (25–40 W) workout inbetween. Patients also participated in daily stretching and respiratory exercises (30 min), exercises in the pool (15 min) and nordic walk (60 min). Stress relief program including massages and baths was also at patients' disposal. All patients took part in the educational program, which provided information about the importance of pharmacological therapy, changes in lifestyle and healthy diet, since mandatory cardioprotective diet is usually not a part of CR programs in Slovenia.

2.2.2. Cardiac stress testing

We performed a cardiac stress test on a stationary exercise bicycle ergometer (cycloergometry) for each patient before entering and at the end of CR program. During the cycloergometry, we raised the load for 25 W every 3 min. The testing was terminated when the patients reached the sub-maximal value for their heart rate (85% of the maximal heart rate), complained of dyspnea or pain (in the chest or other parts of the body), due to exhaustion, if we found ischemic changes in the ECG, bundle branch block, hypertensive reaction or if arrhythmias appeared. Almost all patients from our study had undergone exercise testing already before the discharge from the hospital or during previous course of the disease, thus at the inclusion to CR the exercise testing could not be effected by learning bias.

2.2.3. Cardioprotective diet rich on natural antioxidants

Of all 41 patients, 21 were included in the diet group. They agreed and were highly motivated to strictly follow diet recommendations and not to eat anything else but the food advised and supervised by a clinical dietitian, which was individually prepared for them. The diet group was initially larger but during the course of study 6 patients withdraw: 2 because of acute enterocolitis, 1 because of acute gout attack, one because of adverse reactions of the diet (digestion problems and allergic reactions to nuts) and 2 because of personal reasons. None of the patients from control group withdrew from the study. Each patient from the diet group had a meeting with a clinical dietitian, who assembled an individual menu according to patient's weight, body composition, presence of diabetes and personal preferences. Since we wanted to compose a cardioprotective diet, which would include our national healthy foods, we not only balanced the diet according to caloric intake and percentage of macronutrients, but also enriched it with 300 g of apples and 30 g of raw nuts daily from integrated, high quality Slovenian