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Effects of a nutraceutical combination (berberine, red yeast rice and policosanols) on lipid levels and endothelial function randomized, double-blind, placebo-controlled study

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Abstract *Background and aims:* Some nutraceuticals are prescribed as lipid-lowering substances. However, doubts remain about their efficacy. We evaluated the effects of a nutraceutical combination (NC), consisting of 500 mg berberine, 200 mg red yeast rice and 10 mg policosanols, on cholesterol levels and endothelial function in patients with hypercholesterolemia.

Methods and results: In this single centre, randomized, double-blind, placebo-controlled study, 50 hypercholesterolemic patients (26 males and 24 females, mean age 55 ± 7 years, total cholesterol 6.55 ± 0.75 mmol/l, BMI 28 ± 3.5) were randomized to 6 weeks of treatment with a daily oral dose of NC (25 patients) or placebo (25 patients). In a subsequent open-label extension of 4 weeks, the whole sample received NC. The main outcome measure was decrease total cholesterol (C) levels in the NC arm. Secondary outcome measures were decreased low-density lipoprotein cholesterol (LDL-C) and triglyceride levels, and improved endothelial-dependent flow-mediated dilation (FMD) and insulin sensitivity in relation to NC. Evaluation of absolute changes from baseline showed significant reductions in NC versus placebo for C and LDL-C (C: -1.14 ± 0.88 and -0.03 ± 0.78 mmol/l, $p < 0.001$; LDL-C: -1.06 ± 0.75 and -00.4 ± 0.54 mmol/l, $p < 0.001$), and a significant improvement of FMD ($3 \pm 4\%$ and $0 \pm 3\%$ respectively, $p < 0.05$). After the extension phase, triglyceride levels decreased significantly from 1.57 ± 0.77 to 1.26 ± 0.63 mmol/l, $p < 0.05$ and insulin sensitivity

Acronyms: NC, nutraceutical combination; PL, placebo; FMD, Flow-mediated dilation test; C, lower total cholesterol; LDL-C, LDL-cholesterol; CVD, Cardiovascular diseases; eNOS, endothelial nitric oxide synthase; EPCs, endothelial progenitor cells; Tg, Triglycerides; RYR, Chinese red yeast rice.

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improved in a patient subgroup with insulin resistance at baseline (HOMA: from 3.3 ± 0.4 to 2.5 ± 1.3, $p < 0.05$). No adverse effect was reported.
Conclusions: This NC reduces cholesterol levels. The reduction is associated with improved endothelial function and insulin sensitivity.

Introduction

Atherosclerosis is the leading cause of cardiovascular diseases (CVD), which, in turn, are the main causes of morbidity and mortality in the industrialized world [1]. Conditions that frequently predispose to atherosclerosis, such as hypercholesterolemia, diabetes and arterial hypertension, are associated with endothelial dysfunction. Endothelial dysfunction is an early step of CVD and contributes to plaque initiation and progression [2]. Impaired endothelial function leads to a proinflammatory and prothrombotic phenotype that plays a pivotal role in the development and progression of atherosclerosis and its clinical complications. A hallmark of endothelial cells exposed to hypercholesterolemia is a reduced capacity to release endothelium-derived relaxing factors because of low-density lipoprotein (LDL) promotion of eNOS down-regulation [3]. Lowering cholesterol levels appears to improve endothelial function [4]. In diabetes and insulin resistance, other mechanisms may trigger endothelial dysfunction. Insulin signalling is altered in these two conditions, and affects the pathway leading to phosphorylation and activation of endothelial nitric oxide synthase (eNOS), which is, also in this case, dramatically down-regulated [5].

The NCEP III guidelines recommend the use of statins to lower lipid levels to prevent CVD [6,7]. However, discontinuation rates are high, and almost one-third of statin users discontinue therapy within one year from beginning [8]. The reasons for nonadherence remain speculative, but copayment level, sex, age, number of medications, race and tolerance appear to be the main determinants [9,10]. Furthermore, the use of statins to reduce cardiovascular risk in clinical practice is rarely encouraged for primary prevention.

Lipid-lowering effects have been claimed for some nutraceuticals. However, these compounds have been poorly investigated and many doubts remain as to whether they could be an effective alternative to statins. A meta-analysis of natural therapies for hyperlipemia concluded that policosanols have more effective lipid-lowering properties than plant sterols [11]. Other recognized natural products, like Chinese red yeast rice (RYR), have been demonstrated to be effective and safe in the management of hyperlipemia [12]. In addition, berberine, a natural plant alkaloid, is not only effective in lowering lipids and in the treatment of type 2 diabetes [13], but it also upregulates the number and function of circulating endothelial progenitor cells (EPCs), leading to increased nitric oxide production and endothelial function [14].

Policosanol (10 mg), RYR (200 mg; 3 mg monacolin K) and berberine (500 mg) are the components of a pre-mixed nutraceutical combination (NC) approved in Italy to control dyslipidemia. Previous studies showed that these three substances, used separately, at therapeutic doses, lowered cholesterol levels [11–13]. Consequently, it is conceivable that the single components of the combination, although at low doses, by acting in different points of the lipid metabolic pathway, could lower total cholesterol (C), LDL-cholesterol (LDL-C) and triglycerides (Tg) levels. Moreover, berberine has been found to improve glucose metabolism in diabetes and insulin resistance [13,15]. Therefore, the aim of this study was to investigate the lipid-lowering efficacy of this mixture, to assess its effect on endothelial function and to test whether it affects insulin resistance, in patients with hypercholesterolemia.

Methods

This was a monocentric, 6-week, randomized, double-blind, placebo-controlled study followed by an extension of 4 weeks during which all subjects assumed NC in an open-label design. The primary endpoint was the reduction of C levels in the NC arm. Secondary end points were the reduction of LDL-C and Tg levels, and improvement of endothelial-dependent dilation and insulin sensitivity indices in relation to NC. The study was conducted in accordance with the guidelines of the declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the University of Naples Federico II. Written informed consent was obtained from each subject. Fifty patients were enrolled in the study. Twenty-five were randomly assigned to the NC arm and 25 to the placebo arm.

The inclusion criteria were (1) C level > 5.68 mmol/l (220 mg/dl) and (2) LDL-C level > 3.36 mmol/l (130 mg/dl); and (3) age between 18 and 70 years. Patients with concomitant arterial hypertension or thyroid disease were admitted provided their clinical conditions and treatment had been stable during the previous 3 months at least. We excluded from the study: (1) subjects with proven intolerance to NC compounds; (2) pregnant women and women planning to conceive; (3) patients treated with lipid-lowering products (drugs or other compounds) during the previous 6 weeks; and (4) patients with serum Tg concentration > 5.64 mmol/l (500 mg/dl).

At the screening visit, all patients were instructed to follow a normocaloric and hypolipidic diet (approximately 2000 calories consisting of 55% carbohydrates, 20% proteins, and 25% lipids) during a run-in period of 4 weeks, after which all patients who met the study criteria, as clinically evaluated, were randomized to receive a tablet of NC or placebo once a day after supper, in addition to the normocaloric and hypolipidic diet. The tablet of placebo, identical in taste and appearance to the NC tablet, consisted of inactive compound. Randomisation and blinding were provided by Rottapharm S.p.A (Monza, Italy).