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Testing the Short-Term Efficacy of a Lipid-Lowering Nutraceutical in the Setting of Clinical Practice: A Multicenter Study

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ABSTRACT The main guidelines for cardiovascular disease prevention suggest that nutraceuticals could be an efficacious tool to improve lipid pattern. Our aim was to carry out a clinical trial comparing the metabolic effects of a combined nutraceutical containing both red yeast rice and polyunsaturated fatty acids (PUFAs) and a phytosterol-based approach in a setting of clinical practice. This was a multicenter open study with parallel control. We consecutively enrolled 107 pharmacologically untreated subjects affected by primary polygenic hypercholesterolemia and metabolic syndrome, assigned to 8-week treatment with a combined treatment with red yeast rice (Dif1Stat®, including 5 mg monacolin K) and 610 mg PUFAs. A parallel group of 30 subjects with similar characteristics was treated with phytosterols 1600 mg/die. In the combined nutraceutical group, compared with the baseline level, we observed a significant decrease in total cholesterol (TC; –42.50 ± 18.1 mg/dL), low-density lipoprotein cholesterol (LDL-C; –37.6 ± 13.6 mg/dL), triglycerides (TG; –19.8 ± 25.1 mg/dL), and non-HDL-C (–43.1 ± 17.7 mg/dL) (all $P < .001$). In the phytosterol-treated group, compared to the baseline level, we observed a significant decrease in TC (–13.7 ± 4.3 mg/dL), LDL-C (–17.6 ± 8.5 mg/dL), and non-HDL-C (–14.1 ± 5.6 mg/dL) (all $P < .001$). When comparing the combined nutraceutical effect with that of phytosterols, we observed that the combined nutraceutical intake was associated with a significantly higher decrease in TC, LDL-C, TG, and non-HDL-C (all $P < .001$). In the short term, a combined nutraceutical containing red yeast rice and PUFAs is well tolerated and efficacious in reducing plasma lipid levels in subjects affected by primary polygenic hypercholesterolemia and metabolic syndrome.

KEY WORDS: • ***dietary supplements*** • ***hypercholesterolemia*** • ***monacolins*** • ***nutraceuticals*** • ***phytosterols*** • ***PUFA*** • ***red yeast rice***

INTRODUCTION

THE MAIN RISK FACTORS of cardiovascular disease (CVD) are well known, and reversing the exposure to these risk factors is associated with a significant reduction of CVD risk. This is particularly evident when hypercholesterolemia is treated: a 1 mmol/L decrease in low-density lipoprotein (LDL)-cholesterolemia is associated with a 20% risk reduction of CVD events.[1] However, not all recent literature agrees on the cost-benefit ratio associated with statin treatment in subjects in primary prevention for CVD.[2] A certain number of patients therefore refuse to continue the standard treatment due to intolerance to it,[3] or look for alternative treatments because of their fear of statin-related side effects.[4]

A large amount of literature suggests that numerous natural products could have interesting preventive activities in the management of human hyperlipidemia.[5]

Based on the positive results reported in literature, the European Food Safety Authority (EFSA) recognized that there is a cause-and-effect relationship between the consumption of monacolin K from red yeast rice (daily dose about 10 mg monacolin K) and the maintenance of normal blood low-density lipoprotein cholesterol (LDL-C) concentrations,[6] and between omega-3 polyunsaturated fatty acid (PUFA) intake (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] about 250 mg per day) and normal cardiac function.[7] In this context, our aim was to carry out an open clinical trial comparing the metabolic effects of a combined nutraceutical

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containing both red yeast rice and PUFAs and a phytosterol-based approach in patients affected by primary polygenic hypercholesterolemia and metabolic syndrome.

MATERIALS AND METHODS

This was a multicenter open study with parallel control.

For this study we consecutively enrolled 107 pharmacologically untreated subjects (M: 58, F: 49) affected by primary polygenic hypercholesterolemia and metabolic syndrome,[8] nondiabetic, in primary prevention for CVD.

All patients were already followed for dyslipidemia by specialized lipid clinics, and as they already followed an overall correct diet, they were therefore directly assigned to an 8-week therapy with the combined treatment being tested, containing red yeast rice (Dif1Stat®, including 5 mg monacolin K)[9] and 610 mg PUFAs (of which, 183 mg EPA, 122 DHA), provided by Difass International Srl.

A parallel group of 30 subjects affected by primary polygenic hypercholesterolemia and metabolic syndrome was also enrolled and treated for 8 weeks with phytosterols 1600 mg/die, administered in the form of a yogurt with added phytosterols (Danacol®, Danone Italia). The choice of phytosterols as a treatment for the control group was based on suggestions made by Italian and European guidelines[10,11] for dyslipidemia management, and the dosage of 1600 mg/day was based on the widely available marketed yogurt with this dosage, also considered as risk effective.[12]

The characteristics of the enrolled patients at the baseline are resumed in Table 1. The two groups of patients resulted cross-matched by baseline age, blood pressure, lipid, and glucose metabolism parameters.

Safety monitoring included physical examination, vital sign assessment, weight and height measurements, questioning about adverse events, and laboratory tests. Medication compliance was assessed by counting the number of drug doses returned at clinic visits.

Table 1. Baseline Main Characteristics of the Subjects Included in the Two Treatment Groups

	Combined nutraceutical group (N = 84)		*Phytosterol group (N = 30)*	
	Mean	*SD*	*Mean*	*SD*
Age (years)	52.9	11.8	51.7	12.1
BMI (kg/m^2)	26.1	2.9	26.2	3.0
WC (cm)	90.6	8.2	91.3	8.3
TC (mg/dL)	258.5	13.9	256.9	12.1
HDL-C (mg/dL)	48.6	10.1	49.5	9.8
TG (mg/dL)	197.8	75.3	194.9	69.3
LDL-C (mg/dL)	169.8	16.5	167.6	17.4
Non-HDL-C (mg/dL)	209.8	11.7	208.1	13.2
GOT (U/L)	23.2	7.5	24.8	6.2
GPT (U/L)	24.4	7.7	25.4	7.6
CPK (U/L)	122.7	44.1	128.0	47.5

BMI, body mass index; CPK, creatinine-phosphokinase; GOT, glutamate oxaloacetate transaminase; GPT, glutamate piruvate transaminase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Adverse events, intercurrent diseases, and compliance were also checked at the end of the study.

The whole study was carried out in the field of the routine clinical practice of the units involved in the research, following the internal guidelines of the service, and in line with the principles outlined in the Declaration of Helsinki (Recommendations guiding physicians in biomedical research involving human subjects). All the involved subjects gave written informed consent to the study.

For the statistical analysis, we excluded those patients who were not compliant with the diet and/or the treatment, so that the final sample included 84 subjects (M: 41, F: 43). The data were entered in an apposite database and statistically analyzed with the help of SPSS 21.0, version for Windows. A complete descriptive analysis of all studied parameters was carried out (range, mean, standard deviation, mean standard error, Kurtosis, Skewness), followed by a Kolmogorov-Smirnov normality test. The comparative analysis was carried out applying the ANOVA test followed by *post-hoc* Tukey's test to evaluate treatment associated changes, while the *t*-test for unpaired samples was used to evaluate possible differences between genders or between patients with and without metabolic syndrome. To be more prudent, a P value of less than .01 was considered as significant for all tests.

RESULTS

Both treatments were well tolerated, and no patients had side effects or withdrew from the study. No safety parameters

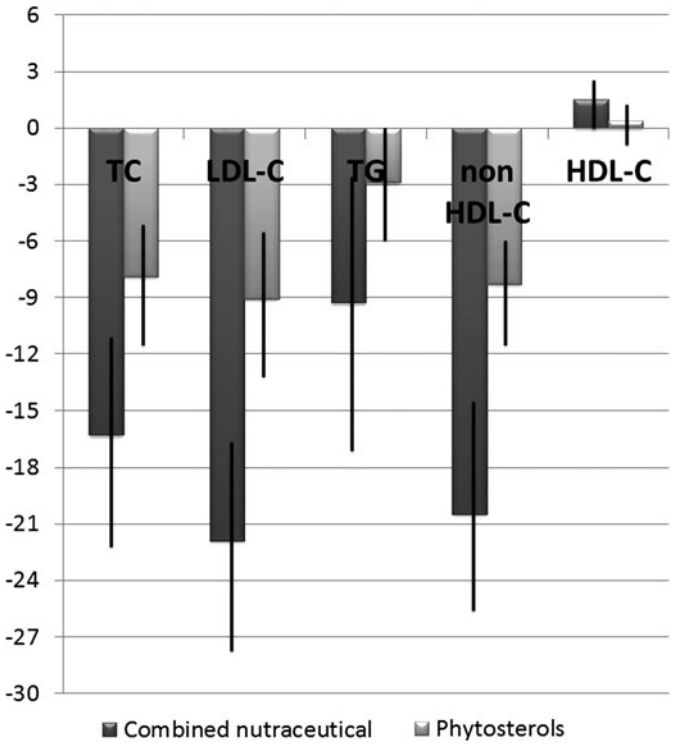

FIG. 1. Main % changes occurred during the study in lipid profile after treatment with the combined nutraceutical being tested and phytosterols.

(GOT, GPT, and CPK) changed significantly during the study. No significant body changes were observed during the study in either of the treatment groups.

The main changes that occurred in lipid profile during the study following both treatments are resumed in Figure 1. In the combined nutraceutical group, compared with the baseline level, we observed a significant decrease in total cholesterol (TC; −42.50 ± 18.1 mg/dL, $P < .001$), LDL-C (−37.6 ± 13.6 mg/dL, $P < .001$), triglyceride (TG; −19.8 ± 25.1 mg/dL, $P < .001$), and non-HDL-C (−43.1 ± 17.7 mg/dL, $P < .001$).

In the phytosterol-treated group, compared with the baseline level, we observed a significant decrease in TC (−13.7 ± 4.3 mg/dL, $P < .001$), LDL-C (−17.6 ± 8.5 mg/dL, $P < .001$), and non-HDL-C (−14.1 ± 5.6 mg/dL, $P < .001$). TGs were not significantly modified in this group.

High-density lipoprotein cholesterol (HDL-C) level was not significantly modified in either the combined nutraceutical or the phytosterol-treated groups.

In comparing the combined nutraceutical effect with that of phytosterols, we observed that the combined nutraceutical intake was associated with a significantly higher decrease in TC ($P < .001$), LDL-C ($P < .001$), TG ($P < .001$), and non-HDL-C ($P < .001$) with respect to the control group.

In the combined nutraceutical group, 75% of subjects reached an LDL-C target of less than 160 mg/dL and 25% of less than 130 mg/dL. In the placebo group, 50% of subjects reached an LDL-C target of less than 160 mg/dL, and none less than 130 mg/dL.

Repeating the analysis by subgroups, similar trends were observed in men and women and in subjects with or without metabolic syndrome. We noted a greater decrease in TG levels only in subjects with baseline TG > 150 mg/dL treated with the combined nutraceutical being tested, who reached a 11% reduction ($P < .001$ vs. subjects with baseline TG < 150 mg/dL).

DISCUSSION

CVDs are still the most common cause of death and one of the main causes of disability in industrialized countries, and despite efforts toward primary prevention, many patients still remain at risk.[13] Lifestyle interventions such as diet and/or physical activity remain the most cost-effective approach in delaying or preventing the onset of CVDs,[14] especially in relatively healthy subjects.[15] Weight loss (reduction of 7–10% of weight) and moderate intensity exercise, such as walking 5–7 days per week, could be useful tools to help blood pressure, LDL-C, and blood glucose control. Giving up smoking is also recommended. However, lifestyle programs are often difficult to follow for long periods, and some risk parameters, such as cholesterolemia, are relatively resistant to changes in dietary habits and physical activity.[16] On the other hand, a relatively large number of dietary supplements and nutraceuticals have been studied for their supposed or demonstrated ability to safely improve lipid patterns in humans.[4,5]

In our study, carried out on moderately hypercholesterolemic subjects with metabolic syndrome, we observed that the intake of a combined nutraceutical containing red yeast rice and PUFAs was associated with a significant reduction of TC (−16% ± 2%), LDL-C (−22% ± 3%), TG (−9% ± 5%), and non-HDL-C (−21% ± 3%), and a significant increase in HDL-C (+1.5% ± 0.5%), without the modification of safety parameters. The observed improvement in TC, LDL-C, and non-HDL-C was also significant when compared with that registered in a parallel group of patients treated with phytosterols. Based on current evidence, we could estimate that an LDL-C reduction of 20% is associated with a reduction in CVD events of about 20% in the following 10 years.[17] Naturally, this is only an indirect estimation, but it supports a potential role for the use of efficacious nutraceuticals in CVD risk reduction.

The improvement in LDL-cholesterolemia is quantitatively similar to that observed in other studies carried out on combined nutraceuticals with lipid-lowering activity, containing either statin-like substances[18] or other components.[19] The lack of a significant improvement in TG level is probably related to the large spontaneous variation of this parameter, the relatively normal level of TG in the patients studied, and the small amount of EPA/DHA included in the tested nutraceutical, aimed more at improving the dietary intake of EPA/DHA for an adequate CVD prevention[7] than at reducing triglyceridemia.

Our study has certain limitations. The first are the relatively small sample of enrolled patients and the short duration of observation. This was, however, just a preliminary study aiming to evaluate efficacy and tolerability. A further limitation is that we did not test the lipid-lowering efficacy of the single components of the nutraceutical to be tested. These are, however, known from available literature.[4] Furthermore, our evaluation of efficacy is based on a limited quantity of laboratory data and on no instrumental data. Another problem is that the study we designed was not a randomized, double-blind clinical trial, although the considered control group had characteristics similar to the main one, and treatment with phytosterols is currently suggested as a first step nutraceutical treatment by a number of experts.[20,21] This choice was also related to the technical difficulty in creating an active comparator similar to a mix of red yeast rice and PUFAs. In fact, our aim was not to compare the effect of the combined nutraceutical being tested with a placebo (the lipid-lowering effect of both red yeast rice and PUFAs being widely known from available literature), but with an active compound also known for its cholesterol-lowering effect.

In conclusion, in the short term the tested combined nutraceutical is well tolerated and efficacious in reducing plasma lipid levels in subjects affected by primary polygenic hypercholesterolemia and metabolic syndrome.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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