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Exploring the Role of Nutraceuticals (Red Yeast Rice) in Secondary Prevention: A New Pathway Can Be Opened

Santiago de Dios[1*], Eduardo Fernandez Carrion[2], Javier Antona Makoshi[3], Juan Jose Parra Fuertes[4], Hector Fleites[1], Eduardo Zatarain[5], Jose Luis Zamorano Gomez[1]

[1]Department of Cardiology, Hospital Universitario de la Zarzuela, Madrid, Spain
[2]Department of Maths, Universidad Complutense, Madrid, Spain
[3]Department of Cardiology, Hospital Conde Valle-Suchil, Madrid, Spain
[4]Department of Cardiology, Hospital 12 de Octubre, Madrid, Spain
[5]Department of Cardiology, Hospital Gregorio Marañón, Madrid, Spain
Email: *drdedios@gmail.com

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Abstract

Background: Long-term survival in acute coronary syndrome has increased steadily in the last decades. Follow-up studies developed in this patient clearly reveal that they are at risk of suffering a new event, placing them in a new stage, secondary prevention. Assuming this increased risk, the control target of their cardiovascular risk factors become more ambitious. In this field, control of Cholesterol levels, particularly LDL-C, has arisen as a priority objective in patients with coronary arterial disease. In this sense, management of dyslipidemia guidelines, recently recognises the role of functional food, highlighting among them is the Red Yeast Rice (RYR). The aim of the study is to establish the potential role of functional food, in secondary prevention, while determining its additional capacity to reduce LDL-C in patients that despite optimal classic treatment (maximum tolerated dose of stain plus Ezetimibe) is still out of control objectives. **Results and Discussion:** 88 patients were included and after 3 months of treatment with RYR, their lipid profiles were compared with the baseline. The variation of T-Col, LDL-C and Trig were statistically significant. A reduction in LDL-C was 10.73 mg/dL, which means a 10.93% of additional reduction over the standard therapy the patients were receiving. Concerning security, no relevant side effects were reported when adding RYR, even in a relevant percentage (35.4%), myalgia disappeared (especially when reducing the titrating dose of the statin). **Conclusion:** Adding RYR in secondary prevention patients in combination with the usual treatment, seems to be an effective alternative to optimize LDL levels and thus gets closer to the target set in the guidelines, without adding relevant side effects, and even improving tolerance

to the statins.

Keywords

Lipids, Nutraceuticals, Coronary Artery Disease, Secondary Prevention

1. Introduction

The survival rate of the acute coronary syndrome has increased in a relevant and sustained way over recent decades. On the one hand, the appearance of new treatments (new antiplatelet agents and anticoagulants, new generation of stents), as well as the implementation of clinical guidelines and management strategies (generalization of primary angioplasty, heart attack code), leave us with a new scenario which is initially more favourable; in which our patients survive their first coronary event.

Follow-up studies of these patients clearly reveal that they are at risk of suffering another event, placing them in a new stage, secondary prevention.

Assuming this increased risk, cardiovascular risk factor control targets become more ambitious. In this stage, the control of Cholesterol, particularly LDL-C, has become one of the priority objectives in cardiology in patients with Coronary Artery Disease (CAD) [1]. Important studies carried out with statins have shown that reductions in LDL-C have a prognostic impact for which they have become the cornerstone of lipid-lowering treatment, especially in secondary prevention.

Recently, other lipid-lowering agents (Ezetimibe in the IMPROVE-IT study, evolocumab and alirocumab in Fourier and Odyssey) have shown that reductions in LDL (in addition to or substitution of statins) also achieve reductions in events, and even in mortality [2] [3].

Therefore, it seems that regardless of the drug used, if LDL-C reductions are obtained, a prognostic improvement in this group of patients will be achieved.

In this sense, the guidelines focused on the management of dyslipidemia, including as part of the treatment, along with the use of drugs, the improvement of general measures, such as diet and exercise. Recently, the relevance of so-called functional foods has also been recognized and increased, highlighting among them is Red Yeast Rice (RYR) or berberine [1].

Despite the availability of various options for reducing LDL-C, a significant percentage of patients in secondary prevention is outside the control target, explained in part by the frequent intolerance to high doses of existing drugs (statins) or the difficulty in accessing new ones (iPCSK9) [4] [5].

Therefore, it seems relevant to have new strategies available to optimize the lipid profile of patients in secondary prevention.

2. Objectives

There is sufficient evidence of the ability of red yeast to lower LDL-C levels in

primary prevention, but its efficacy in secondary prevention is currently unknown [6].

The aim of the study is to determine the role of functional foods, in particular red yeast rice, in secondary prevention.

To determine the additional capacity to reduce LDL-C in patients who, despite optimized classical lipid-lowering therapy (maximum tolerated dose of statins together with ezetimibe), are not within control targets.

3. Methodology

It is a prospective observational study.

Secondary prevention patients were included (had suffered an acute coronary event or had established Coronary Artery Disease (CAD)) and were on statin treatment at the maximum tolerated dose at the time of inclusion.

Data was collected from clinical history (CVRF, comorbidities, CAD).

After starting treatment with a nutraceutical composed of red yeast, berberine and Coenzyme Q10, LDL-C levels were compared retrospectively before and after starting treatment with RYR (after 3 months of treatment).

The appearance (or disappearance) of side effects prior to starting and during treatment was reflected.

4. Results and Discussion

Eighty-eight patients who met the inclusion criteria were included, of which 83 completed the follow-up. The baseline characteristics of the patients are shown in Table 1. The mean follow-up was 132 days (±37).

29.54% of the patients were on concomitant treatment with ezetimibe and 60.22% had received high-intensity statins (atorvastatin > 40 mg, or rosuvastatin > 10 mg).

In almost 10% of patients, the statin dose was reduced (due to side effects)

Table 1. Basal characteristic of the sample population.

Hypertension	62.5%	Stroke	11.36
DM	27.27%	High intensity statin	60.22%
Renal failure	7.95%	Concomitant treatment with ezetimibe	29.54%
Tabaquism	Current 11.36% Former 40.90%	Side effects	35.22% (87.09% Myalgia)
A fibrillation	15.90%	Event last year	12.5%
CAD	Stable angina		19.31%
	Unstable angina		5.6%
	NSTEMI		26.13%
	STEMI		37.50%

when starting RYR treatment.

Statistic Analysis

The different variables in the blood samples were studied in relation to the lipid profile (to assess the efficacy) and the possible side effects of the treatment (safety): Total cholesterol (ColT), LDL.C HDL.C, triglycerides (Trig), GOT, GPT, GGT, CPK, creatinine (creat), glycosylated haemoglobin A1c (HbglicA1c), blood glucose (gluc).

An analysis was carried out using the Wilcoxon non-parametric test (WSR), carried out for a confidence interval of 5%: a p-value < 0.05 rejects the hypothesis that the objective variable has a similar distribution before and after the study.

Table 2 shows the changes in the mean values of the parameters analysed.

The baseline LDL-C level was 97.33 mg/dL. The variation of ColT-LDL-C and Trig was statistically significant (Figure 1). The reduction in LDL.C was 10.73 mg/dL, which means an additional 10.93% reduction over the standard therapy that patients were already receiving. If those patients in whom the baseline statin dose was modified (reduced due to side effects) were excluded from the analysis, the reduction was similar. In fact, exclusively analysing these patients, (they were only 9.1%), they also presented a reduction in LDL.C (12.35 mg/dL, 9.84%), but in this they almost did not reach significance statistics. With this reduction in LDL levels, an additional 16.8% of the patients entered the LDL-C control target, which at the time the study was designed was 70 mg/dL according to the ESC guidelines).

Col-T was reduced by 10.25 mg/dL. The reduction in Trig was 12.35 mg/dL. There was no statistically significant variation in HDL-C or any other parameter analysed.

Table 2. Mean value (and standard deviation) at baseline and at the end. Significance value of Wilcoxon Signed-Rank (WSR) test.

Variables	Baseline	Final	Difference	Units	p-value (WSR)
T-Col	175.47 (31.64)	165.22 (36.21)	−10.25	mg/dL	0.0000115
LDL-C	98.09 (24.02)	87.36 (2.09)	−10.73	mg/dL	0.000000017
HDL-C	47.9 (15.51)	47.21 (15.32)	−0.69	mg/dL	0.99
Trig	125.44 (60.23)	113.09 (55.39)	−12.35	mg/dL	0.00097
Creat	0.97 (0.25)	0.99 (0.29)	0.02	mg/dL	0.07
HbGlicA1c	5.92 (0.56)	6.02 (0.95)	0.10	mg/dL	0.68
Gluc	101.23 (17.92)	103.58 (23.12)	2.25	mg/dL	0.25
GOT	28.99 (14.3)	27.24 (10.35)	−1.75	U/L	0.24
GPT	29.63 (13.23)	27.23 (11.49)	−2.40	U/L	0.26
CPK	123.98 (67.84)	124.27 (73.81)	0.29	U/L	0.83
LDL-C (dose change)	100.38 (17.61)	91.62 (12.98)	−8.76	mg/dL	0.18

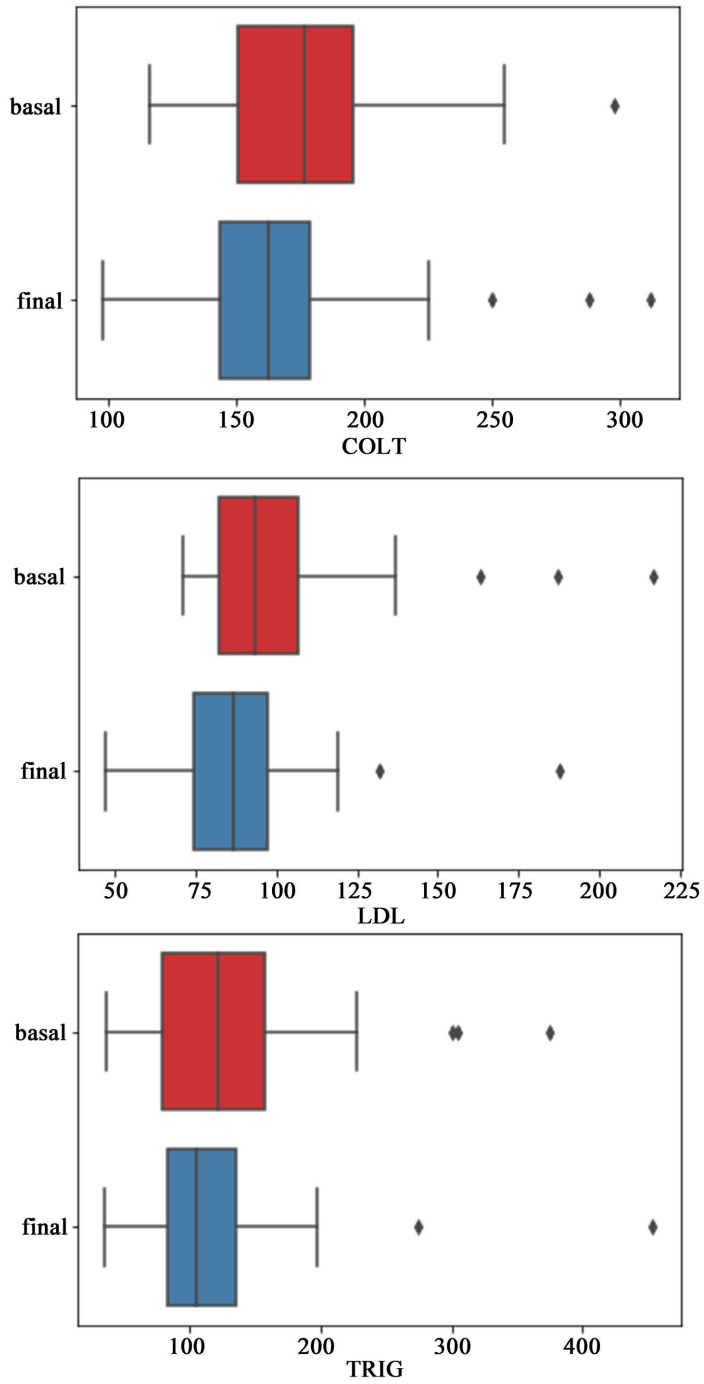

Figure 1. Baseline and final distribution of ColT, LDL-C y Trig.

In relation to safety, 35.2% of the patients presented side effects at baseline (mainly myalgia). This is certainly a higher percentage than that observed in other studies with statins, but this is probably due to the fact that the selection of patients for the study has favoured the fact that since they already have side effects, the statin dose titration was not considered (or attempts were even made to reduce it), but the possibility of adding RYR was. In no patient were there side effects or significant alterations at the analytical level of liver function, kidney func-

tion, or blood glucose levels. Myalgias were also not reported (no CPK elevation was shown), they even disappeared in several patients (especially when the statin dose was reduced): in 35.4% of the patients the side effects (elevated transaminases, myalgias) that they presented disappeared.

5. Conclusion

Adding red yeast rice in secondary prevention patients in combination with the usual treatment, seems to be an effective alternative to optimize LDL levels and thus gets closer to the target set in the guidelines, without adding relevant side effects, and even improving tolerance to the statins. Although the number of patients included in the study is undoubtedly limited and it is an observational study, it could represent an alternative for those patients who are not at target levels and are not candidates for PCSK9 inhibitors, or for those whose statin dose may not be titrated or even reduced (and kept on target) for side effects. Randomised studies with a larger population are necessary to confirm these claims.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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