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Effects of Armolipid Plus on small dense LDL particles in a sample of patients affected by familial combined hyperlipidemia

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Abstract

Aim—The aim of this study was to test small dense LDL changes with Armolipid Plus treatment in patients with familial combined hyperlipidemia (FCHL).

Methods—After 4 weeks, 30 patients with FCHL were included in an 8-week, randomized, double-blind study and were taking, in addition to the standard diet, either placebo or Armolipid Plus.

Results—The placebo group showed no statistically significant differences in the studied parameters; instead, in the Armolipid Plus group, statistically significant reduction differences were detected in BMI ($p = 0.010$), LDL score ($p = 0.035$) and an increase in mean LDL particle diameter ($p = 0.040$).

Conclusion—The combination of a standard diet with Armolipid Plus is able to reduce LDL score and increase LDL particle diameter in a group of FCHL after 8 weeks of treatment.

Keywords

Armolipid Plus; familial combined hyperlipidemia; small dense LDL

Familial combined hyperlipidemia (FCHL) is a common metabolic and inherited hyperlipidemia, with a prevalence in general populations of 1% [1].

FCHL is a heterogeneous disorder at high cardiovascular disease (CV) risk [2]: the affected subjects have elevated plasma cholesterol or triglycerides (Tg) levels, or both. Lipid profile is frequently associated with an unfavorable decrease in HDL concentration, an elevated apolipoprotein (apo) B and an increased prevalence of atherogenic, small dense LDL (sd-LDL) subfractions [3].

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Ethical conduct of research The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Several large, prospective studies in general populations, using gradient gel electrophoresis to determine LDL particle size, confirmed the relationship of sd-LDL with coronary events [4–6]. FCHL is susceptible to considerable improvements with the change in lifestyle, especially eating habits. The basics of dietary treatment are: reduction of energy intake (in case of excess weight), decrease of saturated fat favoring the use of monounsaturated fats (olive oil), increase in complex carbohydrates with slow absorption and increased amount of soluble fibers [7,8].

Armolidip Plus (MEDA-Rottapharm S.p.A., Monza, Italy) is a nutraceutical combination that contains red yeast rice (RYR) extract (with 3 mg of monacolin K), berberine, policosanols, folic acid, coenzyme Q10 and astaxanthin [9].

Some of these components exert effects favoring the control of plasma cholesterol and Tg when administered in addition to a diet generally adequate for this purpose [10]. Even though statin therapy is the mainstay of primary and secondary prevention of CV complications in FCHL [1], we investigated a nutraceutical approach to treat this kind of patients; in particular, we evaluate the effects of Armolidip Plus on serum sd-LDL in addition to an adequate diet therapy.

Methods

Study population

A total of 30 FCHL patients (23.3% women), who had been admitted to the outpatient Lipid Clinic of the 'Federico II' University of Naples and who accepted to participate to this study, were enrolled, after excluding patients with secondary causes of dyslipidemia or using any drug known to affect lipid metabolism.

FCHL was diagnosed according to the metabolic criteria suggested by an Italian Expert Panel [11]: serum triglyceride (Tg) >200 mg/dl and/or apo B >130 mg/dl and/or LDL-cholesterol (LDL-C) >160 mg/dl in the pro-band, plus phenotype variability in at least one first-degree relative, with or without history of premature cardiovascular disease (CVD) in the pro-band and/or in first-degree relatives.

The study was designed as a randomized, double-blind, placebo-controlled trial.

After 4 weeks of normocaloric/fiber-rich diet (45–55 g/day), with approximately 2000 kcal for man and 1700 kcal for women, consisting of 54% carbohydrates, 16% proteins and 30% lipids (6% saturated fatty acid, 21% monounsaturated fat, 3% polyunsaturated) and 160 mg/day of cholesterol, patients were randomly assigned to receive either Armolidip Plus (MEDA-Rottapharm SpA; 1 tablet/day, containing 200 mg of RYR [equivalent to 3 mg of monacolin K], 500 mg of berberine, 10 mg of policosanols, 0.2 mg of folic acid, 2.0 mg of coenzyme Q10 and 0.5 mg of astaxanthin; RYR contained in Armolidip Plus was citrinine and aflatoxins free) or placebo (1 tablet/day, identical in taste and appearance to the Armolidip Plus tablet but containing microcrystalline cellulose, iron oxide brown 70, Compritol E ATO [Gattefoss_e, Saint-Priest, Lyon, France] and magnesium stearate) for 8 weeks.

By the time of the blood sampling, at randomization visit (week 0) and at final visit (week 8), none of the study participants reported or showed any inflammatory or other concurrent diseases.

Since there was no gender difference in the affected relatives of the FCHL probands, a possible explanation for the significantly higher prevalence of men in our sample is a self-selection due to their own awareness of being at higher CVD risk than women. The study was conducted in accordance with the guidelines of the Declaration of Helsinki, all participants signed an informed consent and the protocol of the study was approved by the Ethics Board of the 'Federico II' University of Naples.

Clinical & biochemical assessment

Anthropometric measurements were made with the subjects in indoor clothing and without shoes. BMI, used as a measure of general obesity, was calculated as weight (kg) divided by squared height (in m²). Waist circumference, an index of abdominal obesity, was measured midway between the bottom of the rib cage and the top of the iliac crest. Sitting brachial blood pressure was measured two-times after a 5-min rest using a sphygmomanometer. A standard questionnaire was used to collect information about smoking habits. Blood specimens were collected after a 12–14-h fast, from 8:00 to 9:30 a.m., to reduce the influence of circadian variation. Total cholesterol and Tg concentrations were measured by using standard enzymatic methods [12,13]. HDL-cholesterol (HDL-C) was measured after the precipitation of very LDLs and LDLs with phosphotungstic acid [14], and LDL-C was calculated according to the Friedewald formula. Fasting glucose levels were enzymatically determined by the peroxidase method. Apo B was measured with turbidimetric assay with an automated method (Cobas-Mira, Roche, Italy). The error of these methods was evaluated by daily analyzing a plasma pool and resulted to be <5%.

LDL particle size determination

LDL particles separation was performed by Lipoprint System (Quantimetrix Inc., CA, USA). This method is based on electrophoresis of lipid-stained serum (Sudan black) in nondenaturing gel gradient of polyacrylamide. Seven LDL subfractions of decreasing size and increasing density and electrophoretic mobility (Rf) are obtained. The coefficients of inter- and intra-assay variations for cholesterol distribution in the seven LDL species were less than 10% for both. Mean LDL particle diameter (MPD) is calculated on the basis of the different areas under the curve of the seven LDL species with different electrophoretic mobility [15]. The proportion of sd-LDL particles (subfractions 3–7) to the whole LDL area (subfractions 1–7) was also calculated in our sample (LDL score) [16]. The diameter of the LDL particles at the cutoff point separating subfractions 1–2 from subfractions 3–7 was 25.1 nm. LDL score has been shown to be significantly related to coronary heart disease in multivariate analysis [17–19] and proved to be significantly related to MPD in the studied population (n = 228; Spearman rho = 0.885; p < 0.001).

Statistical analyses

Continuous variables were described as mean and standard deviation and categorical variables were reported in frequencies and percentages; all statistical analyses were performed with SPSS version 13.0 (SPSS, Inc., IL, USA). All differences between week 0 and week 8 were assessed by paired Student's t test, or nonparametric Wilcoxon Signed Ranks Test. p-value for comparison of Armolipid Plus versus placebo was evaluated with the general linear model for repeated measures. p-values < 0.05 were considered as statistically significant.

Results

Physical and biochemical characteristics of the study participants (n = 30) at randomization visit (week 0), after 4 weeks of standard diet, are displayed in Table 1. 23.3% of total population were women. As expected, patients showed elevated cholesterol and Tg level and low HDL-C levels.

After 8 week of treatment with placebo or Armolipid Plus, patients underwent a fasting blood sampling for a second biochemical screening.

Thirteen patients in Armolipid Plus group had a compliance greater than 80%, excepted one patient with a compliance of 50%. One patient of Armolipid Plus group was lost to follow up at week 8.

Table 2 shows the clinical and biochemical differences between placebo group and Armolipid Plus group at randomization and at final visit. In placebo group, no statistically significant differences were detected in studied parameters between week 0 and week 8; instead, in Armolipid Plus group, statistically significant differences reductions were detected in BMI (p = 0.010), and LDL score (p = 0.035) and an increase in MPD (p = 0.040).

A comparison of studied parameters between placebo group and Armolipid Plus group was also performed: BMI (p = 0.004), waist circumference (p = 0.026) and diastolic blood pressure (p = 0.024), LDL score (p = 0.033) and MPD (p = 0.021) resulted statistically different between the two groups.

Figure 1 shows changes of LDL score in Armolipid Plus group and placebo group. In Armolipid Plus group, LDL score decreased by 28% between week 0 (LDL score = 24%) and week 8 (LDL score = 17.3%) (p = 0.035); in contrast, LDL score decreased in placebo group only of 16% between week 0 (LDL score = 19.6%) and week 8 (LDL score = 16.5%) (p = 0.233).

Figure 2 shows modifications of MPD in Armolipid Plus group and placebo group. MPD significantly increased in Armolipid Plus group from 261.4 Å at week 0 to 264.1 Å at week 8 (p = 0.040). In placebo group, the MPD increased from 263.6 Å at week 0 to 264.9 Å at week 8, with no statistical significance (p = 0.181).

Discussion

The main finding of this study is that association between a standard diet and Armolipid Plus is able to reduce sd-LDL score and increase LDL particle diameter in a group of familial combined patients after 8 weeks of treatment.

sd-LDL particles are significantly associated with increased triglyceride and apo B levels and decreased HDL-C and apo A-I levels, and with higher CV risk and atherosclerosis [16,19,20]. The significant reduction of sd-LDL particles and increase of LDL diameter (as shown in Figures 1 & 2) represent a major achievement in terms of CV risk reduction in the group treated with Armolipid Plus with respect to the group treated with placebo.

Several studies have already investigated the role of Armolipid Plus in treatment of dyslipidemia: Ruscica *et al.* [9] in a randomized, double-blind and crossover study showed that, in 30 patients with moderate dyslipidemia and metabolic syndrome, treatment with Armolipid Plus led to a significant reduction of total cholesterol, and LDL-C, similar to pravastatin, and an increase of HDL-C [9].

Solà *et al.* [21] in a randomized, double-blind, parallel, placebo-controlled multicenter trial showed that in 102 patients with low CV risk at 12 weeks, Armolipid Plus reduced LDL, apo B-100 and total cholesterol/HDL ratio, the Apo B/apo A-I ratio, while increasing apo A-I. Armolipid Plus was also associated with modest mean weight loss compared with control group, while dietary composition remained unchanged in the Armolipid Plus group [21].

We did not observe significant quantitative changes in serum lipids. However, this was partly expected based on the spontaneous variability of the lipid pattern in FCHL patients and on the small sample of patients involved in our trial; moreover, the main aim of our study was to evaluate the change in LDL atherogenicity in a subpopulation with high CV risk, because of higher level of sd-LDL, relatively high cholesterol level and major tendency in development of atherosclerosis [3–6]. To the best of our knowledge, this is the first study that investigates Armolipid Plus effects on a group of FCHL patients.

A supposed mechanism of the lipid-lowering effects of Armolipid Plus is due to the synergic effect of RYR, berberin, policosanol, astaxanthin, coenzyme Q10 and folic acid. RYR extract, in particular monacolin K, has an inhibitory activity on HMG-CoA reductase. Furthermore, RYR contains beta-sitosterol and campesterol, which might suppress adipogenesis by regulating a transcription factor in 3T3-L1 cells and decreasing glycerol-3-phosphate dehydrogenase activity [22].

Berberine has been suggested to lead to an increased expression and half-life of the LDL receptor (LDLR) on the surface of hepatocytes [23]. By activating JNK/c-jun pathway, berberine increased the transcriptional activity of the LDLR promoter and, by acting on ERK signalling pathway, it stabilizes LDLR mRNA [24].

The role of policosanol in lipid lowering is not clear: it seems to play a role in the downregulation of cellular expression of HMG-CoA reductase [24]. Moreover, policosanol

could have pleiotropic effect, also acting by slowing LDL oxidation, by inhibition of platelet aggregation and smooth muscle cell proliferation [26].

Therefore, nutraceuticals such as Armolipid Plus may supply lifestyle changing in patients with FCHL, and possibly it could be an alternative therapeutic approach in patients that cannot receive a first-line pharmacological treatment, for instance patients intolerant to statins, even in association with other pharmacological treatments [27,28]. Principal limitation of this study is the sample size (n = 30): additional studies with higher numerosity are needed to confirm our results.

Future studies to compare Armolipid Plus effects to low statin doses are necessary.

We observed a significative difference in BMI, waist circumference and diastolic pressure between Armolipid Plus group and placebo group. This result is in line with a previous study [21] and it may be due to berberine effects [29,30]

Conclusion

The present study shows that a small dose of RYR associated with berberine and other nutraceutical compounds (Armolipid Plus) is capable to reduce LDL score and to increase LDL particle size in a group of patients with clinical diagnosis of FCHL.

Future perspective

This paper can be useful in treatment of patient with FCHL who cannot receive a first-line pharmacological treatment, for instance patients intolerant to statins, even in association with other pharmacological treatments.

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Executive summary

- This paper demonstrated that association between standard diet with Armolipid Plus is able to reduce LDL score and increase LDL particle diameter in a group of patients with familial combined hyperlipidemia.
- Familial combined hyperlipidemia is a common metabolic and inherited hyperlipidemia with prevalence of atherogenic, small dense low-density lipoprotein and at high cardiovascular disease risk.
- Small dense LDL are associated with coronary events.
- This study showed that Armolipid Plus is capable to reduce LDL score and to increase LDL particle size in a group of patients with clinical diagnosis of familial combined hyperlipidemia.

Figure 1. Modifications of LDL score

(A) Armolipid Plus group (n = 14) and (B) placebo group (n = 15). Values are expressed as mean $\pm$ standard deviation.

Figure 2. Modifications of mean LDL size
(A) Armolipid Plus group (n = 14) and (B) placebo group (n = 15).

Table 1

Main baseline clinical and biochemical characteristics of studied population (n = 30) at randomization visit (week 0).

Characteristics	Week 0
Women (%)	23.3
Age (years)	44.1 ± 13.0
BMI (kg/m ²)	26.2 ± 2.8
Waist circumference (cm)	94.6 ± 9.6
Systolic blood pressure (mmHg)	122.7 ± 10.7
Diastolic blood pressure (mmHg)	78.0 ± 7.5
Total cholesterol (mg/dl)	235.3 ± 41.4
Triglycerides (mg/dl)	247.3 ± 101.7
LDL-C (mg/dl)	149.3 ± 45.3
HDL-C (mg/dl)	39.5 ± 7.9
Apo B (g/l)	1.3 ± 0.2
Fasting glucose (mg/dl)	92.3 ± 12.8
LDL score (% small dense LDL)	21.8 ± 13.9
Mean LDL particle diameter (A)	262.5 ± 5.0

Values are expressed as mean ± standard deviation.

Table 2

Clinical and biochemical differences between placebo group and Armolipid Plus group at randomization visit (week 0) and final visit (week 8).

Characteristics	Week 0 placebo (n = 15)	Week 8 placebo (n = 15)	p-value within group difference	Week 0 Armolipid Plus (n = 15)	Week 8 Armolipid Plus (n = 14)	p-value within group difference	p-value for comparison of Armolipid Plus vs placebo
BMI (kg/m ²)	26.7 ± 2.8	26.5 ± 3.0	0.243	26.0 ± 2.8	25.4 ± 2.9	0.010	0.004
Waist circumference (cm)	97.3 ± 8.5	96.8 ± 8.9	0.323	92.0 ± 10.2	91.3 ± 9.7	0.051	0.026
Systolic blood pressure (mmHg)	122.5 ± 9.2	122.2 ± 13.9	0.497	123.0 ± 12.3	121.8 ± 11.0	0.074	0.130
Diastolic blood pressure (mmHg)	78.1 ± 6.9	76.7 ± 7.6	0.060	77.9 ± 8.3	76.0 ± 7.3	0.206	0.024
Total cholesterol (mg/dl)	241.9 ± 42.1	244.2 ± 42.8	0.835	228.8 ± 41.1	223.6 ± 49.2	0.400	0.728
Triglycerides (mg/dl)	204.2 ± 80.9	270.5 ± 159.0	0.060	290.3 ± 104.3	242.0 ± 94.4	0.137	0.666
LDL-C (mg/dl)	162.8 ± 41.2	150.7 ± 40.7	0.144	134.7 ± 46.5	132.7 ± 45.4	0.263	0.073
HDL-C (mg/dl)	38.2 ± 9.1	39.3 ± 10.2	0.336	40.8 ± 6.6	42.4 ± 5.9	0.374	0.188
Apo B (g/l)	1.3 ± 0.2	1.3 ± 0.2	0.650	1.2 ± 0.2	1.2 ± 0.2	0.667	0.532
Fasting glucose (mg/dl)	93.0 ± 5.9	94.8 ± 8.0	0.362	91.5 ± 17.5	96.8 ± 13.8	0.147	0.077

Values are expressed as mean ± standard deviation.