Nutrition 58 (2019) 7–10

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Effect of resveratrol supplementation on lipid profile in subjects with dyslipidemia: A randomized double-blind, placebo-controlled trial

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ARTICLE INFO

Article History:
Received 5 March 2018
Received in revised form 6 June 2018
Accepted 9 June 2018

Keywords:
Resveratrol
Lipid profile
Lipids
Dyslipidemia
Randomized controlled trial

ABSTRACT

Objectives: The aim of this study was to explore the effect of resveratrol supplementation on lipid profile in individuals with dyslipidemia.
Methods: Apparently healthy men and non-pregnant women 20 to 65 y of age with new diagnosis of dyslipidemia were enrolled in a randomized double-blind, placebo-controlled trial and randomly allocated to receive either resveratrol 100 mg/d or placebo (sucrose 0.5 g/d) for 2 mo. Smoking, alcohol intake, diabetes, acute or chronic renal or hepatic diseases, malignancy, cardiovascular disease, serum triacylglycerol levels ≥400 mg/dL, low-density lipoprotein cholesterol levels ≥190 mg/dL, and consumption of lipid-lowering drugs or supplements containing resveratrol were exclusion criteria.
Results: Seventy-one individuals with new diagnosis of dyslipidemia were enrolled and randomly allocated to the resveratrol (n = 35) or placebo groups (n = 36). At baseline, there were no significant differences between the study groups. After intervention period, individuals in the resveratrol group showed a significant decrease in total cholesterol (201.4 ± 34.4 versus 220.6 ± 37.4, $P = 0.04$) and triacylglycerol (133.4 ± 55.3 versus 166.7 ± 68.5, $P = 0.04$) concentrations compared with the placebo group, without significant statistical differences for high-density lipoprotein cholesterol and low-density lipoprotein cholesterol levels.
Conclusion: The results suggest that resveratrol supplementation significantly reduces total cholesterol and triacylglycerol concentrations in individuals with dyslipidemia.

Introduction

It is well known that elevated concentrations of circulating lipids are a strong risk factor for cardiovascular disease (CVD) [1]; in this regard, the high levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), or triacylglycerols (TGs), as well as the low concentrations of high-density lipoprotein cholesterol (HDL-C) are consistently associated with the risk for future CVD [2–4], and their interactions exert a cumulative effect in the increasing cardiovascular mortality [5,6]. Therefore, given the high prevalence of dyslipidemia worldwide, the search of complementary therapies to treat lipid abnormalities in high-risk populations emerges as a priority.

Resveratrol is a natural polyphenolic compound that exhibits beneficial health effects such as antithrombotic, anticancer, antiosteoporotic, antimicrobial, and antioxidant activities [7,8]. It is a stilbene derivative produced by plants and is mainly found in grapes and red wine. In this regard, the French paradox revealed that the moderate consumption of red wine, which contains significant counts of resveratrol, is associated with low incidence of CVD in the French population despite a high intake of saturated fats [9]. Thus, it has been postulated that resveratrol may exert a potential cardioprotective action on the atherosclerotic process [10]. However, although experimental studies have reported a lipid-lowering effect of resveratrol [11,12], results of clinical trials are inconsistent and scarce; therefore, the aim of this study was to explore the effect of resveratrol supplementation on the lipid profile in individuals with dyslipidemia.

Material and methods

Previous approval by the Ethical and Research Committee from the Mexican Social Security Institute, in accordance with the ethical principles of the Declaration of Helsinki and after obtaining written informed consent of the participants, a randomized double-blind, placebo-controlled clinical trial was conducted. Apparently healthy men and non-pregnant women 20 to 65 y of age from the general population of Durango, a city in northern Mexico, were invited to participate in the study.

This work was supported by the Instituto Mexicano del Seguro Social (grant no: FIS/IMSS/PROT/G15/1434). The authors have no conflicts of interest to declare.
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https://doi.org/10.1016/j.nut.2018.06.015
0899-9007/

Exclusion criteria included the presence of smoking, alcohol intake, previous diagnosis of diabetes, acute or chronic renal or hepatic diseases, malignancy, CVD, and consumption of lipid-lowering drugs or supplements containing resveratrol, as well as serum TG levels ≥400 mg/dL (4.5 mmol/L), and LDL-C levels ≥190 mg/dL (4.9 mmol/L).

Thus, individuals with new diagnosis of dyslipidemia were enrolled and randomly allocated to receive either resveratrol (Veratrol, Gelpharma, Jalisco, Mexico; trans-resveratrol 100 mg/d) or placebo (sucrose 0.5 g/d) for 2 mo. The preparation of resveratrol that was used in this trial was extracted from *Polygonum cuspidatum* and included dibasic calcium phosphate and magnesium stearate as excipients. A list of random numbers generated by computer was used to assign participants in the study groups. Supplementation and placebo capsules were provided in identical bottles and capsules. Also, based on a total daily caloric intake of 30 kcal/kg of ideal body weight, the individuals of both groups were advised to consume a diet with 50% carbohydrates, 30% lipids, and 20% proteins, and to perform physical activity for ≥30 min three times per week. Clinical and biochemical parameters were measured at baseline and after 2 mo of treatment.

Adherence to treatment, diet, exercise, and the presence of adverse effects were monitored every month by capsule count and personal interviews. Participants and personnel involved in the outcome measurements were blinded to the group assignment.

Sample size was calculated using a statistical power of 80%, α value of 0.05, and based on the difference in means of TC levels between the intervention and control groups (20 mg/dL) [13]. The estimated sample size was 30 individuals for each group.

Definitions

Dyslipidemia was defined by the presence of either TC concentrations ≥200 mg/dL (5.2 mmol/L) and/or TG levels ≥150 mg/dL (1.7 mmol/L) [14].

Measurements

In the standing position and fasting conditions, weight, height, and waist circumference (WC) were measured using a fixed scale with stadiometer (Tanita TBF-215, Tokyo, Japan) with the participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. WC was measured to the nearest centimeter using a flexible tape; the anatomic landmarks were the midway between the lowest portion of the rib cage and the superior border of the iliac crest [15]. Blood pressure was measured as suggested by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [16].

Assays

A whole blood sample was obtained from the antecubital vein after 12-h overnight fasting. The serum glucose was measured using the glucose-oxidase method with intra- and interassay variation coefficients of 1.1% and 1.5%. TC and TGs were enzymatically determined by spectrophotometric methods. HDL-C fraction was measured after precipitation by phosphotungstic reagent and then determined in the supernatant. The intra- and interassay coefficients of variation were 1.8% and 2.6% for TC, 1.7% and 3.1% for TGs, and 1.3% and 2.6% for HDL-C. LDL-C fraction was calculated by the Friedewald formula [17]. Finally, non–HDL-C concentrations were estimated by subtracting HDL-C from TC.

Statistical analysis

Numerical values are expressed as mean ± SD and categorical variables are reported as proportions.

Differences between the groups were estimated using two-way analysis of variance with Bonferroni post hoc test for numerical parameters and χ^2 test for categorical variables. Furthermore, intragroup differences were assessed by paired Student's *t* test (Mann–Whitney U test for skewed data).

Statistical significance was considered by $P < 0.05$ and 95% confidence interval (CI). Data were analyzed using the statistical package SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

We screened 282 apparently healthy individuals; 211 were excluded because they did not fulfill the inclusion criteria or refused to participate. Thus, 71 individuals with new diagnosis of dyslipidemia were enrolled and randomly allocated to the resveratrol (n = 35) or placebo groups (n = 36). There were nine dropouts (all due to lost to follow-up), four in the resveratrol group and five in the placebo group. Thereby, 62 individuals successfully completed the study follow-up and were analyzed (Fig. 1).

In both study groups, no adverse effects were documented during the follow-up period.

At baseline, there were no significant differences between the resveratrol and placebo groups for age (42.2 ± 10.8 versus 42.7 ± 11.1, $P = 0.85$), women (70.9 versus 77.4%, $P = 0.77$), total body fat percentage (34.3 ± 8.6 versus 37.6 ± 7.8, $P = 0.11$), respectively.

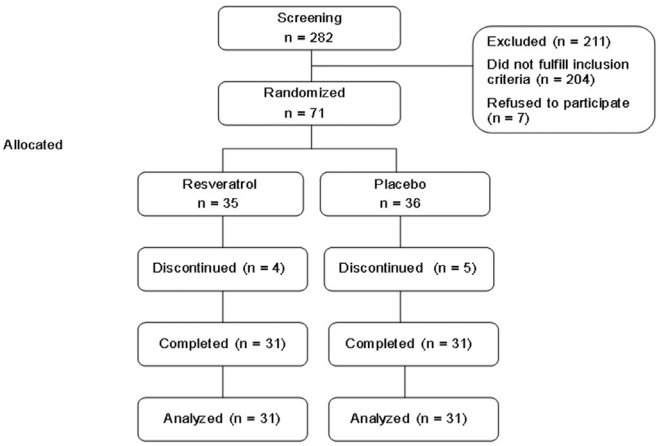

Fig. 1. Flow diagram of the trial.

Table 1
Clinical and biochemical characteristics of the study groups by sex at baseline

	Resveratrol Women (mean ± SD)	Men (mean ± SD)	*P*-value	Placebo Women (mean ± SD)	Men (mean ± SD)	*P*-value
N	22	9		24	7	
Body mass index, kg/m^2	28.1 ± 5	27.4 ± 3.9	0.71	29.7 ± 6.4	29.3 ± 4.1	0.86
Waist circumference, cm	89.1 ± 11.3	99.6 ± 8.6	0.01	94.3 ± 12.6	100.5 ± 12.1	0.26
Systolic blood pressure, mm Hg	114.7 ± 12.1	115.2 ± 7.9	0.89	111.3 ± 13.8	114.1 ± 12.4	0.62
Diastolic blood pressure, mm Hg	70.5 ± 7.5	73.2 ± 13.4	0.59	71.6 ± 11.1	72.4 ± 9.1	0.85
Glucose, mg/dL	91.3 ± 8.8	95.2 ± 10.2	0.33	95.3 ± 11	95.1 ± 11.5	0.96
Total cholesterol, mg/dL	222.8 ± 25.6	229.2 ± 25.7	0.53	221 ± 23.5	216.2 ± 36.6	0.75
HDL cholesterol, mg/dL	51.6 ± 10.5	52.2 ± 11.1	0.89	52.5 ± 13.8	43.2 ± 9.2	0.057
LDL cholesterol, mg/dL	141 ± 22.4	142.7 ± 19.7	0.84	136.6 ± 17.3	146.6 ± 25.5	0.36
Non-HDL cholesterol, mg/dL	171.2 ± 28.6	177 ± 26	0.59	168.5 ± 19.6	173 ± 34.8	0.75
Triacylglycerols, mg/dL	150.6 ± 66.2	171.3 ± 87.9	0.53*	159.5 ± 56.7	132.1 ± 68.1	0.35*

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
**P*-value estimated using U Mann–Whitney test.

Table 2
Clinical and biochemical characteristics between the study groups

	Baseline Resveratrol (mean ± SD)	Placebo (mean ± SD)	Final Resveratrol (mean ± SD)	Placebo (mean ± SD)	*P*-value*,†	*P*-value*,‡	*P*-value*,§
N	31	31	31	31			
Body mass index, kg/m^2	27.9 ± 4.7	29.6 ± 5.9	27.5 ± 4.6	29.1 ± 5.5	0.42	0.77	0.12
Waist circumference, cm	91.9 ± 11.5	95.7 ± 12.6	91.2 ± 10.6	95.4 ± 12.8	0.51	0.64	0.65
Systolic blood pressure, mm Hg	114.8 ± 10.9	112 ± 13.4	112.7 ± 11.2	111.5 ± 13.7	0.15	0.74	0.10
Diastolic blood pressure, mm Hg	71.3 ± 9.4	71.8 ± 10.5	70.7 ± 7.9	73.0 ± 8.7	0.23	0.66	0.15
Glucose, mg/dL	92.4 ± 9.2	95.3 ± 10.9	90.6 ± 12.6	94.6 ± 9.6	0.40	0.79	0.93
Total cholesterol, mg/dL	224.6 ± 25.4	220 ± 26.3	201.4 ± 34.4	220.6 ± 37.4	0.04	0.03	0.01
HDL cholesterol, mg/dL	51.7 ± 10.5	50.4 ± 13.3	50.2 ± 9.6	52.8 ± 13.4	0.16	0.69	<0.001
LDL cholesterol, mg/dL	141.5 ± 21.4	138.8 ± 19.4	124.5 ± 33.4	134.4 ± 31.7	0.23	0.95	0.001
Non-HDL cholesterol, mg/dL	172.9 ± 27.6	169.5 ± 23.3	151.2 ± 37.8	167.8 ± 36.7	0.42	0.43	0.28
Triacylglycerols, mg/dL	156.6 ± 72.2	153.3 ± 59.4	133.4 ± 55.3	166.7 ± 68.5	0.04	0.04	<0.001

ANOVA, analysis of variance; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
**P*-values estimated using two-way ANOVA with Bonferroni post hoc test.
†*P*-value for treatment (resveratrol vs placebo).
‡*P*-value for time (baseline vs final).
§*P*-value for the intersection.

Clinical and biochemical characteristics of the study groups by sex at baseline are presented in Table 1. In the resveratrol group, men had higher WC than women without significant differences for other variables, whereas in the placebo group there were no significant differences.

Table 2 shows the comparison between the study groups. There were significant differences in TC and TG levels for treatment (resveratrol versus placebo) and time (baseline versus final), whereas significant changes were found in TC, HDL-C, LDL-C, and TG concentrations for the intersection. There were no significant differences for other variables.

At the end of the trial, no significant differences in anthropometric variables were seen between the study groups. Regarding biochemical parameters, individuals in the resveratrol group showed a significant decrease in TC and TG levels compared with the placebo group, without significant statistical differences for HDL-C, LDL-C, and non–HDL-C levels (Table 3).

Table 3
Difference of change in clinical and biochemical parameters between the study groups

	Resveratrol (mean ± SD)	Placebo (mean ± SD)	*P*-value
N	31	31	
Body mass index, kg/m^2	−0.3 ± 1.1	−0.5 ± 1.4	0.22
Waist circumference, cm	−0.6 ± 2.8	−0.3 ± 3.2	0.16
Systolic blood pressure, mm Hg	−2.1 ± 2.8	−0.4 ± 3.5	0.71
Diastolic blood pressure, mm Hg	−0.5 ± 2.2	1.2 ± 2.4	0.29
Glucose, mg/dL	−1.8 ± 2.8	−0.6 ± 2.6	0.16
Total cholesterol, mg/dL	−23.1 ± 7.6	0.6 ± 8.2	0.04
HDL cholesterol, mg/dL	−1.5 ± 2.5	2.3 ± 3.4	0.38
LDL cholesterol, mg/dL	−16.9 ± 7.1	−4.4 ± 6.6	0.23
Non-HDL cholesterol, mg/dL	−21.6 ± 8.4	−1.7 ± 7.8	0.08
Triacylglycerols, mg/dL	−23.1 ± 16.3	13.4 ± 16.2	0.04*

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
**P*-value estimated using U Mann–Whitney test.

Discussion

Results from the present study found that 100 mg/d of resveratrol significantly decreased TC and TG levels in individuals with dyslipidemia.

These findings agree with a previous clinical trial that reported a significant reduction in TC concentration after resveratrol supplementation (250 mg/d) in patients with type 2 diabetes [18]. Hence, the present study adds to the field that the beneficial effect of resveratrol on the TC levels also may be found in healthy individuals, suggesting a potential role of this phenolic compound in prevention of CVDs. The hypocholesterolemic effect of resveratrol may be explained by its phenolic hydroxyls, which result in oxidation of unsaturated fatty acids and decrease in circulating cholesterol [11].

In the same way, a previous clinical trial found significant reduction in plasma TGs after resveratrol supplementation

(150 mg/d) in obese individuals [19]. Several mechanisms, such as changes in medium- and long-chain TG concentrations, decreased apolipoprotein C-III, reduced activity of hepatic acyl-coenzyme A cholesterol acyl-transferase, and the upregulation of genes involved in lipid metabolism [20], might be linked to the hypotriacylglycerolmic effect of resveratrol. Moreover, although there were no significant changes in TG levels in the intragroup analysis, there was a reduction in the resveratrol group. TG concentrations increased slightly in the placebo group reaching significant difference in the intergroup analysis.

Regarding HDL-C, a previous randomized controlled trial did not observe significant changes on HDL-C and LDL-C levels after resveratrol supplementation (150 mg/d) in overweight and obese individuals [21], in agreement with our results. Nevertheless, in the intragroup analysis of the present study, individuals who received resveratrol exhibited a significant decrease in LDL-C levels. In this context, it has been suggested that resveratrol protects LDL particles against peroxidation by antioxidative and chelating activities [22,23]. Also, resveratrol inhibits oxidation of LDL by potent oxidants such as ferrylmyoglobin and peroxynitrite [24]. Furthermore, because resveratrol increases the expression of LDL receptors in hepatocytes, it is expected that this polyphenol might decrease circulating LDL-C levels. In this regard, the lack of effect of resveratrol on LDL-C levels could be related to the treatment duration of 2 mo, which probably was insufficient to demonstrate a positive effect; hence, longer clinical trials are warranted to verify the efficacy of resveratrol on HDL-C and LDL-C levels.

Nonetheless, it is important to note that a previous meta-analysis of randomized controlled trials found no significant effect of resveratrol on lipid profile [25]. This inconsistency may be related to different types and doses of resveratrol used by the included studies in that meta-analysis.

In addition to its effect on lipid metabolism, the antiatherosclerotic activity of resveratrol involves increased activity of peroxisome proliferator-activated receptor α [26], amelioration of glucose metabolism [19], inhibition of platelet aggregation [27], decreased blood pressure [19], mitigation of inflammation [28], and improvement of endothelial function [29]. Thus, it is expected that resveratrol supplementation exerts a potential cardioprotective effect.

Studies in humans evaluating the effect of resveratrol on lipid profile as primary outcome are scarce, which represents the main strength of the present study. Additionally, we included individuals with new diagnosis of dyslipidemia without previous lipid-lowering treatment.

The short treatment duration was probably the main limitation of our trial. Therefore, although there were no side effects during the follow-up period, the long-term events and safety of resveratrol remain to be assured in future studies.

Conclusion

The results of the present study suggest that resveratrol supplementation significantly reduces TC and TG concentrations in individuals with dyslipidemia.

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