Original Article
OBESITY BIOLOGY AND INTEGRATED PHYSIOLOGY

Obesity

Effect of Resveratrol on Blood Lipid Levels in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis

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Objective: Few studies have considered the effect of resveratrol on blood lipid levels, and the results of these studies are inconsistent. In this study, the first meta-analysis on the effect of resveratrol on blood lipid levels in patients with type 2 diabetes was conducted.
Methods: This study used keywords such as type 2 diabetes, total cholesterol, triglyceride (TG), high-density lipoprotein, low-density lipoprotein, and resveratrol and their abbreviations, free words, and related words to search PubMed, Cochrane Library, and Embase. The Cochrane risk of bias tool was used to evaluate the risk of bias, and Review Manager 5.3 and Stata 13.0 were used for data merging and statistical analysis.
Results: Ten randomized controlled trials involving a total of 363 patients with type 2 diabetes were included in the analysis. The results show that longer resveratrol intervention time (≥6 months) can reduce TG levels. But resveratrol increased total cholesterol in patients within obesity range. In type 2 diabetes patients with obesity and in those who took lipid-lowering drugs, resveratrol increased low-density lipoprotein levels.
Conclusions: Resveratrol can improve TG in patients with type 2 diabetes.

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Introduction

The risk of cardiovascular disease is elevated in patients with type 2 diabetes, in association with their high blood pressure, high blood lipid levels, and other risk factors (1). High blood lipid levels affect both the macrovascular system, promoting the occurrence of coronary heart disease and cerebral infarction, and the microvascular system, promoting diabetic microvascular diseases such as diabetic nephropathy and retinopathy. Thus, high blood lipid levels can result in serious damage to systemic blood vessels and organs (2,3). Although statins can influence blood lipid levels, the incidence of vascular events remains elevated after statin therapy.

Resveratrol (3,5,4′-trihydroxystilbene) is a polyphenol with phytoalexin properties belonging to the terpenoids. Resveratrol is found in grapes, peanuts, cranberries, and many other foods including Japanese knotweed (*Polygonum cuspidatum*), which is particularly high in resveratrol and can be used as herb. Studies have shown that resveratrol has a wide range of effects, including antimicrobial (4), anti-inflammatory (5), anti-apoptotic (6), and anticancer (7) effects, and promotes osteogenic factor formation (8). Resveratrol can also play a beneficial role in liver diseases and hepatic steatosis by reducing oxidative stress and hepatic fibrosis (9,10). In addition, resveratrol has antioxidant effects on certain chronic diseases such as diabetes and cardiovascular disease (11).

To date, many animal studies and human clinical studies have been conducted on the effects of resveratrol on blood glucose and insulin sensitivity, and resveratrol's benefits have been gradually confirmed. In a meta-analysis that included 11 randomized controlled trials (RCTs) involving 388 subjects, resveratrol significantly improved glycemic control and insulin sensitivity in diabetic patients but did not affect blood glucose measurements in nondiabetic patients (12). In a 2017 meta-analysis of type 2 diabetes performed by Zhu et al. (13) that included nine RCTs involving 283 subjects, resveratrol significantly reduced fasting blood glucose and homeostatic model assessment of insulin resistance scores and increased insulin levels.

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In view of the beneficial effects of resveratrol on blood glucose and its richness in food, the influence of resveratrol on blood lipids has gradually received attention. However, results of animal studies and clinical trials on the effects of resveratrol on lipid profiles are inconsistent. Therefore, we conducted the first meta-analysis of the effects of resveratrol on blood lipid levels in type 2 diabetes patients.

Methods

Search strategy

We searched the PubMed, Cochrane Library, and Embase databases using keywords such as total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and resveratrol and their abbreviations, as well as free words and other related words. The searches were limited to peer-reviewed studies in the English language. References in relevant articles and reviews were also checked to avoid overlooking any studies. Details of the search strategy are provided in online Supporting Information. All searches were conducted through August 2018.

Literature screening

Documents retrieved in the three databases were imported into the document management software EndNote (Clarivate Analytics). We used the check function of the software to identify and remove duplicate documents. The remaining documents were sorted by year so that further duplicate documents could be identified. Next, articles such as reviews, animal and cell experiments, and case reports were excluded. We read the abstract or the full text and decided whether to include a study according to inclusion and exclusion criteria. Literature screening was independently performed by two authors followed by cross-checking. If there was disagreement, a third author was consulted on whether to include a study.

Inclusion criteria

1. Clinical RCT of parallel or crossover type;
2. Subjects with confirmed type 2 diabetes;
3. No statistical differences in baseline lipid profiles; and
4. Relevant data provided in the literature or obtainable through data conversion.

Exclusion criteria

1. Reviews, case reports, animal experiments, and cell experiments;
2. Nondiabetic patients with impaired glucose tolerance or healthy subjects;
3. Statistical differences in baseline lipid profiles; and
4. Relevant data incomplete or unobtainable, repeated publication, or literature of poor quality.

Data extraction

Two authors read the full text of all articles meeting the criteria, and both authors extracted relevant information for each study, including first author, year of publication, country, mean age and gender of population, BMI, mean glycated hemoglobin, mean fasting blood glucose at baseline, diabetes duration, sample size, loss to follow-up rate, study design, intervention performed on the experimental and control groups, intervention time, evaluation index and results, taking of lipid-lowering drugs, and blood lipid level of the experimental and control groups at the study end point (means ± SD). If no blood lipid–related values were reported after the intervention, they were calculated using baseline values and the postintervention difference or CI. The information extracted by the two authors was compared, and any discrepancies were settled on consultation with the third author.

Risk bias assessment

We used the Cochrane risk of bias tool to evaluate the risk of bias among included studies under seven parameters: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Each entry has three evaluation criteria: low, unclear, and high risk of bias. The assessment was performed independently by two authors, and disagreements were resolved in consultation with a third person.

Statistical analysis

Review Manager 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration) and Stata 13.0 (StataCorp LP) were used for data consolidation and statistical analysis. All blood lipids (TC, TG, HDL, LDL) were considered continuous variables, and their effect indicators were expressed as mean differences (MD) and 95% CIs. The statistical model used the inverse variance weighting methodology. Regarding the analytical model, if the heterogeneity was small, a fixed-effects model was used, and if the heterogeneity was large, a random-effects model was used. Data from the included studies could therefore be consolidated on the basis of homogeneity. Homogeneity (or heterogeneity) was evaluated by Q and I^2 value statistical testing. P values were the focus of Q statistical testing. If $P > 0.1$, the study was considered nonheterogeneous, that is, of sufficient homogeneity, and the data could be consolidated. If $P < 0.1$, the study was considered heterogeneous, meaning that homogeneity was poor and the source of heterogeneity needed to be determined (14). Regarding the I^2 test, according to the *Cochrane Handbook for Systematic Reviews of Interventions* (14), values of $I^2 \leq 50\%$ indicate the heterogeneity is relatively small and that the results are more stable. Values of $I^2 > 50\%$ indicate good heterogeneity, requiring further exploration of the source of that heterogeneity. According to the intervention dose of resveratrol (≥ 1,000 mg/d or < 1,000 mg/d), the intervention time (≥ 6 months or < 6 months), the BMI level (normal: < 25 kg/m^2, overweight: 25-30 kg/m^2, obesity: > 30 kg/m^2), and lipid-lowering drugs (taking lipid-lowering drugs, not taking lipid-lowering drugs, not mentioned), subgroup analyses were performed to analyze the source of heterogeneity. If each group had a $P > 0.1$ Q statistical test or $I^2 < 50\%$, then this factor was the source of heterogeneity. If $P < 0.1$ or $I^2 > 50\%$ for any subgroup, then this factor was not a source of heterogeneity. In addition to subgroup analysis, a sensitivity analysis was performed as an alternative method to identify the source of heterogeneity. Each time a study was removed from the analysis, a new meta-analysis was performed to determine whether there was a change in the effect indicator. If the heterogeneity was significantly reduced after study removal ($P > 0.1$ or $I^2 < 50\%$), this single study was considered to have had a marked influence on the effect indicator and was the source of heterogeneity. An Egger test was used to evaluate publication bias, and plots were prepared using Stata software. If $P > 0.05$, it was considered that publication bias was not present (15).

Results

Document retrieval and inclusion

Through the search of the databases, a total of 330 articles were retrieved. After screening, 10 articles were retained (Supporting Information Figure S1), including 8 randomized, parallel, controlled studies and 2 crossover controlled studies. The systematic review of these 10 studies involved a total of 363 subjects. The intervention dose of resveratrol ranged from 8.1 to 3,000 mg/d, and the intervention time ranged from 1 to 12 months. Of the 10 studies, 5 measured TC, 8 measured TG, 9 measured HDL, and 6 measured LDL. The effects of resveratrol intervention on these indicators by study are shown in Supporting Information Table S1.

Bias risk assessment outcome

The bias risk assessment for the included studies (16-25) is shown in Figure 1. The risk of selection bias, performance bias, attrition bias,

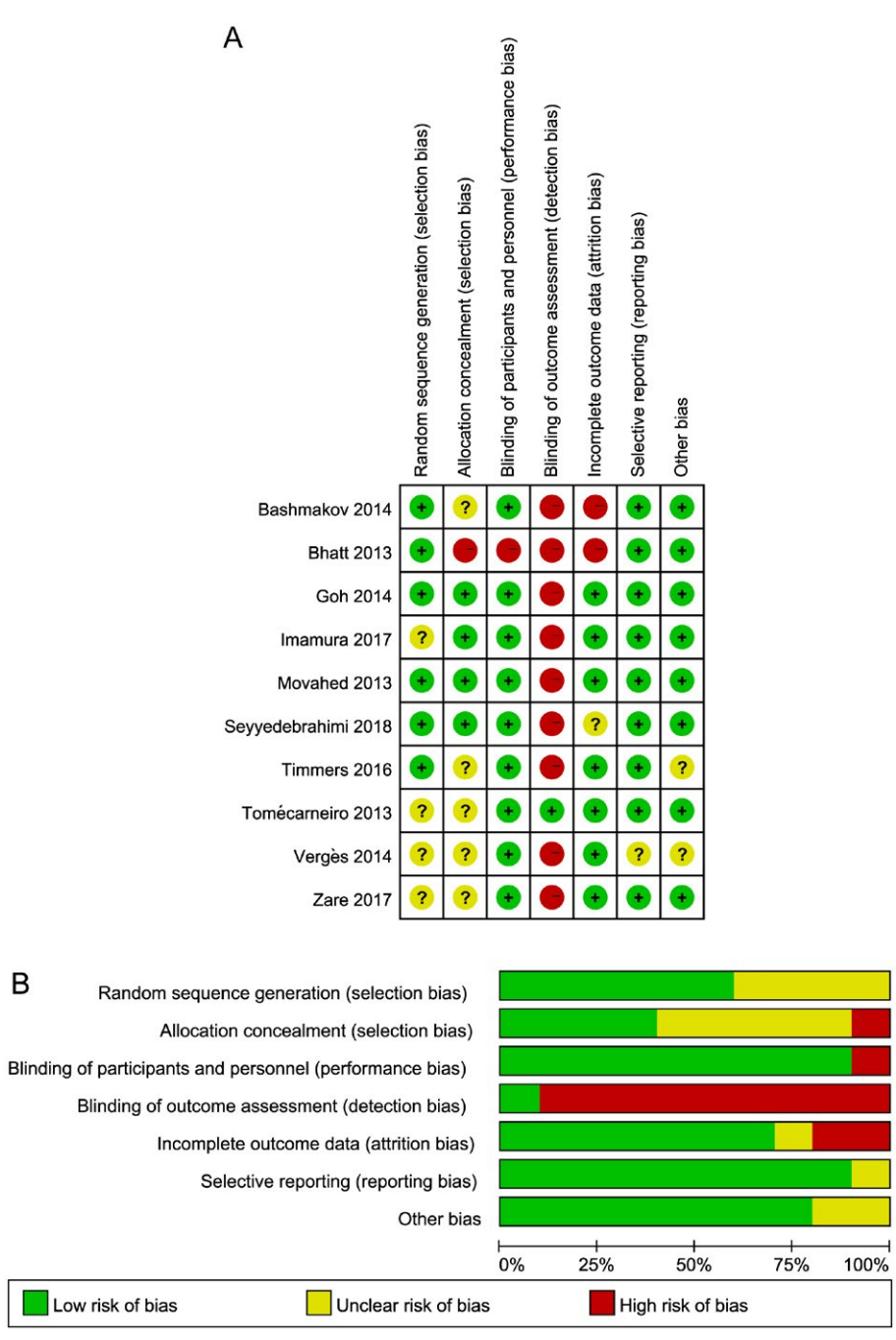

Figure 1 Assessment of bias risk. (A) Risk of bias summary: review authors' judgements about each risk of bias item for each included study. (B) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

TABLE 1 Subject characteristics of included studies

First author	Year	Country	Age	Sex	BMI at baseline (kg/m^2)	HbA_{1c} at baseline (%)	FPG at baseline (mmol/L)	Duration of DM (y)	Sample size	Rate of loss to follow-up
Bashmakov (16)	2014	Egypt	54.0 ± 10.1	M, F	28.42 ± 3.10	-	10.27 ± 4.40	15.1 ± 7.9	24	22.6%
Bhatt (17)	2013	India	57.2 ± 8.8	M, F	24.69 ± 3.29	8.83 ± 1.59	10.46 ± 2.74	7.1 ± 4.6	57	8.1%
Goh (18)	2014	Singapore	56.3 ± 6.0	M	26.90 ± 5.80	8.90 ± 1.20	10.70 ± 2.40	9.5 ± 5.5	10	0.0%
Imamura (19)	2017	Finland	57.8 ± 10.3	M, F	25.10 ± 4.18	7.25 ± 1.26	8.06 ± 2.55	-	50	0.0%
Movahed (20)	2013	Iran	52.1 ± 6.5	M, F	27.43 ± 3.69	8.45 ± 1.41	9.10 ± 2.87	5.6 ± 1.5	64	3.0%
Seyyedebrahimi (21)	2018	Iran	56.8 ± 6.4	M, F	28.94 ± 4.40	-	8.25 ± 1.85	-	46	4.2%
Timmers (22)	2016	Netherlands	63.2 ± 7.9	M	30.50 ± 0.57	6.78 ± 0.20	8.20 ± 0.38	6.8 ± 1.0	17	0.0%
Tomé-Carneiro (23)	2013	Spain	60.6 ± 11.4	M	30.80 ± 4.52	7.24 ± 1.37	8.32 ± 3.28	-	22	0.0%
Vergès (24)	2014	France	-	M, F	35.80 ± 6.70	8.60 ± 1.70	-	-	30	0.0%
Zare (25)	2017	Iran	50.0 ± 8.2	M, F	28.79 ± 4.82	-	8.96 ± 3.00	<5	43	14.0%

Values are expressed as means ± SD.
DM, type 2 diabetes; F, female; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; M, male.

reporting bias, and other bias was low, whereas the risk of selection bias was unclear and the risk of detection bias was high. For single studies, the risk of bias was higher for Bhatt et al. (17), and the remaining studies had low or unclear bias. In general, the quality of the included studies was acceptable.

Subject characteristics, study design, and outcomes

For each of the included studies, the subject characteristics are given in Table 1, and the study design and outcomes are given in Table 2.

Changes in blood lipid levels as a result of resveratrol intervention

TC. Five studies involving 170 participants reported TC measurement. The random-effects model was applied. After combining the effect amounts, the MD was −0.34 mmol/L (95% CI: −0.99, 0.32), and I^2 = 91% indicated heterogeneity (Figure 2). Given that the dose of resveratrol intervention in the included studies was < 1,000 mg/d, subgroup analyses were conducted based on time of intervention, BMI status, and whether lipid-lowering drugs were taken (Table 3, Supporting Information Figures S2-S4). BMI and lipid-lowering drugs were identified as the potential source of heterogeneity, whereas resveratrol administration might increase TC levels in patients with obesity. As only one study was included in the normal and overweight BMI group, the outcome of the subgroup analyses warranted further consideration. Because the study design of Timmers et al. (22) was a crossover trial, whereas the other studies were parallel trials, the removal of Timmers' study after conducting a sensitivity analysis did not reduce the heterogeneity (I^2 = 73%), and P = 0.01, indicating this study was not a source of heterogeneity. P = 0.326 from the Egger test indicated there was no publication bias (Supporting Information Figure S5).

TG. Eight studies involving 322 participants reported TG measurements. There was a large amount of heterogeneity (I^2 = 80%), so the random-effects model was used. The MD of the total effect amount for TG was −0.03 mmol/L (95% CI: −0.38, 0.32) (Figure 3). Subgroup analyses based on resveratrol dose showed that for higher doses (≥ 1,000 mg/d), the MD was 0.34 mmol/L (95% CI: −0.12, 0.80) and I^2 = 32%, and for lower doses (< 1,000 mg/d), the MD was −0.18 mmol/L (95% CI: −0.54, 0.19) and I^2 = 72%, suggesting that resveratrol dose was not a source of heterogeneity in TG outcome (Supporting Figure S6). Subgroup analyses based on resveratrol intervention time showed that for longer interventions (≥ 6 months), the MD was −0.62 mmol/L (95% CI: −1.04, −0.21) and I^2 = 27%, and for shorter interventions (≤6 months), the MD was 0.12 mmol/L (95% CI: −0.08, 0.32) and I^2 = 13%. This indicated that longer resveratrol interventions reduced TG levels in patients with type 2 diabetes and that intervention period was also a source of heterogeneity in TG outcome (Supporting Figure S7). The average BMI of the subjects might be also the source of heterogeneity (Table 4, Supporting Figures S8-S9). There was no publication bias because a value of P = 0.763 was obtained using the Egger test (Supporting Figure S10).

HDL. Nine studies involving a total of 320 participants reported HDL measurements. Resveratrol did not significantly improve HDL in patients with type 2 diabetes, with MD = 0.01 mmol/L (95% CI: −0.04, 0.07), I^2 = 33%, and P = 0.15 in the fixed-effects model (Supporting

TABLE 2 Study design and outcomes of included studies

First author	Study design	Resveratrol group	Control group	Intervention time (m)	Index	Results	Lipid-lowering drugs
Bashmakov (16)	Single-blind, randomized, placebo-controlled, parallel trial	2 × 50 mg/d	Placebo	2	TC, HDL, LDL	Not significant	Yes (some patients)
Bhatt (17)	Open, randomized, controlled, parallel trial	250 mg/d	Empty: control	6	TG, TC, HDL, LDL	All of them decreased	No
Goh (18)	Double-blind, randomized, placebo-controlled, parallel trial	3,000 mg/d	Placebo	3	TG, HDL, LDL	LDL increased	Not mentioned
Imamura (19)	Double-blind, randomized, placebo-controlled, parallel trial	27.97 mg/d	Placebo	3	TG, TC, HDL	Not significant	Yes (some patients)
Movahed (20)	Double-blind, randomized, placebo-controlled, parallel trial	2 × 500 mg/d	Placebo	1.5	TG, HDL	HDL increased	Yes (some patients)
Seyyedebrahimi (21)	Double-blind, randomized, placebo-controlled, parallel trial	2 × 400 mg/d	Placebo	2	TG, HDL	Not significant	Yes (some patients)
Timmers (22)	Double-blind, randomized, placebo-controlled, crossover trial	150 mg/d	Placebo	1	TC, HDL, LDL	TC, LDL decreased	Yes (some patients)
Tomé-Carneiro (23)	Three-blind, randomized, placebo-controlled, parallel trial	8.1 mg/d and 16.21 mg/d, respectively, for 6 mo	Placebo	12	TG, TC, HDL, LDL	Not significant	Yes (some patients)
Vergès (24)	Double-blind, randomized, placebo-controlled, crossover trial	40 mg/d	Placebo	3	TG, HDL, LDL	Not significant	Yes
Zare (25)	Double-blind, randomized, placebo-controlled, parallel trial	240 mg/d	Placebo	1	TG	Not significant	Not mentioned

HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride.

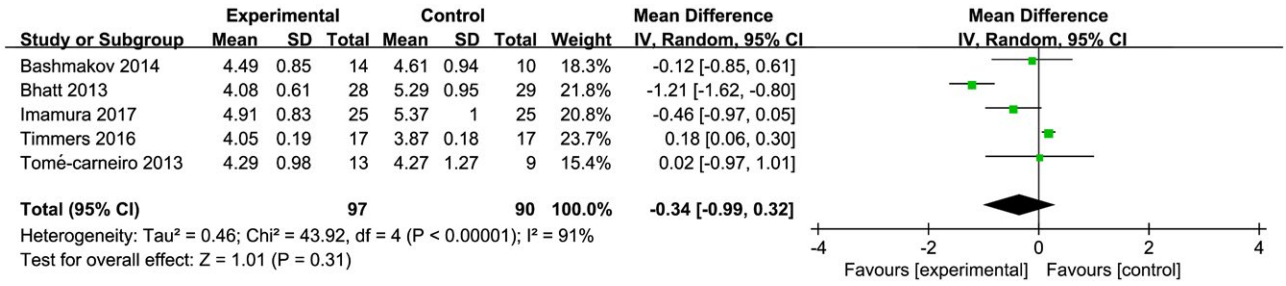

Figure 2 Forest plot comparing the posttreatment total cholesterol levels of the control and resveratrol groups.

Figure S11). *P* was 0.241 (> 0.05) in the Egger test, indicating that there was no publication bias (Supporting Figure S12).

LDL. Six studies involving 160 participants reported LDL measurements. The combined effect of LDL was MD = –0.14 mmol/L (95% CI: –0.56, 0.28), and the heterogeneity was large (I^2 = 84%), so the random-effects model was applied (Supporting Figure S13). Subgroup analyses based on dose, duration of resveratrol intervention, BMI status, and whether lipid-lowering drugs were taken showed that the sources of heterogeneity were BMI and lipid-lowering drugs (Table 5, Supporting Figures S14-S17). The results showed that resveratrol increased LDL in patients with BMI within the obesity range and patients taking lipid-lowering drugs. *P* was 0.510 (> 0.05) in the Egger test, indicating that there was no publication bias (Supporting Figure S18).

Discussion

Our meta-analysis included 10 RCTs involving a total of 363 subjects. When the effect amount of TC was combined, it was found to be heterogeneous. When removing a crossover study and conducting a sensitivity analysis, heterogeneity decreased from 91% to 73%, indicating that the study had homogeneity compared with other studies. Resveratrol dose, duration of resveratrol intervention, subject baseline BMI, and whether lipid-lowering drugs were taken during the resveratrol intervention may affect the final combined effect. Subgroup analyses based on these four factors were performed for lipid measures showing significant heterogeneity when the studies were combined, that is, TG and LDL. Regarding TG, longer intervention periods reduced TG levels. Regarding LDL, resveratrol increased LDL levels in patients with obesity and those who took lipid-lowering drugs. LDL was also increased after shorter resveratrol interventions. As for why resveratrol raises the level of LDL, further exploration is needed. Overall, resveratrol can improve the levels of some blood lipid indicators.

The main source of cholesterol is the exogenous pathway through dietary intake. However, dietary cholesterol has little effect on plasma cholesterol because this is mainly regulated through cholesterol synthesis by the body.

TABLE 3 Subgroup analyses of effect of resveratrol on TC

	No. of studies	MD	95% CI	I^2	Heterogeneity *P*	I^2 between groups	*P* for between-subgroup heterogeneity
Intervention time						96.9%	<0.00001
≥6 mo	2	–1.03	–1.41, –0.65	80%	0.02		
<6 mo	3	0.14	0.02, 0.26	68%	0.04		
BMI						95.4%	<0.00001
Normal (<25 kg/m^2)	1	–1.21	–1.62, –0.80	-	-		
Overweight (25-30 kg/m^2)	1	–0.46	–0.97, 0.05	-	-		
Obesity (>30 kg/m^2)	3	0.17	0.05, 0.29	0%	0.70		
Lipid-lowering drugs						94.2%	<0.00001
Yes	4	–0.05	–0.41, 0.31	52%	0.10		
No	1	–1.21	–1.62, –0.80	-	-		

TC, total cholesterol; MD, mean difference.

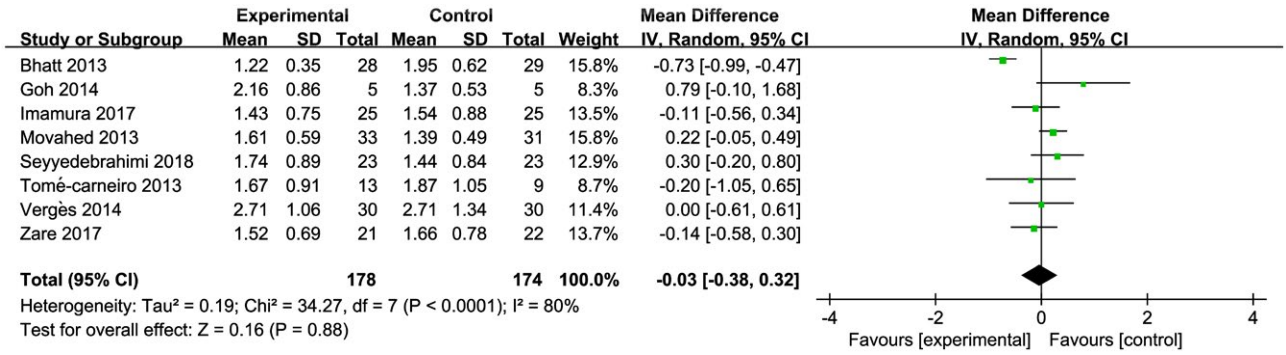

Figure 3 Forest plot comparing the posttreatment triglyceride levels of the control and resveratrol groups.

The beneficial effect of resveratrol on TC may be exerted through the peroxisome proliferator–activated receptor γ and adenosine receptor A2a pathways, which have been shown to increase the induction and expression of cholesterol reverse transporters (26) such as liver X nuclear receptor α, ATP-binding cassette sub-family A member 1 (ABCA1) and G1 (ABCG1), and scavenger receptor class B member I, which are capable of promoting cholesterol efflux, thereby preventing cholesterol accumulation.

Previous studies have shown that 27-hydroxylase expression promotes the elimination of cholesterol through two pathways: the first directly through the catabolism of cholesterol and the second indirectly through the regulation of ABCA1 and apolipoprotein E expression. Resveratrol regulates the expression of the mitochondrial cholesterol metabolizing enzyme cytochrome P450 27-hydroxylase, which in turn promotes the synthesis of 27-hydroxycholesterol, thereby mediating cholesterol clearance through the formation of hydroxysterol (26,27). In addition, 27-hydroxycholesterol has been shown to exert a statin-like action, inhibiting 3-hydroxy-3-methylglutaryl-Coenzyme A reductase and smooth muscle cell proliferation to reduce foam cell formation mediated lipid deposition in the vascular wall (28). In addition, resveratrol may stimulate the transfer of free cholesterol and cholesterol esters from macrophages to lipid-poor receptors such as apolipoprotein A-1 and HDL regulating the expression of major cholesterol transporters (ABCA1, ABCG1, and scavenger receptor class B member I). This process contributes to the formation of mature HDL cholesterol granules and, therefore, promotes the transport of excess cholesterol to the liver and intestinal excretion. Studies have also shown that resveratrol can prevent the conversion of LDL to oxidized LDL, which promotes endothelial dysfunction and atherosclerosis (29).

TABLE 4 Subgroup analyses of effect of resveratrol on TG

	No. of studies	MD	95% CI	I^2	Heterogeneity *P*	I^2 between groups	*P* for between-subgroup heterogeneity
Intervention dose						66.6%	0.08
≥1000 mg/d	2	0.34	−0.12, 0.80	32%	0.23		
<1000 m/d	6	−0.18	−0.54, 0.19	72%	0.003		
Intervention time						90.1%	0.001
≥6 mo	2	−0.62	−1.04, −0.21	27%	0.24		
<6 mo	6	0.12	−0.08, 0.32	13%	0.33		
BMI						91.6%	<0.00001
Normal (<25 kg/m^2)	1	−0.73	−0.99, −0.47	-	-		
Overweight (25-30 kg/m^2)	5	0.13	−0.10, 0.37	28%	0.24		
Obesity (>30 kg/m^2)	2	−0.07	−0.56, 0.43	0%	0.71		
Lipid-lowering drugs						92.8%	<0.00001
Yes	5	0.13	−0.06, 0.32	0%	0.61		
No	1	−0.73	−0.99, −0.47	-	-		
Not mentioned	2	0.24	−0.65, 1.14	71%	0.07		

TG, triglyceride; MD, mean difference.

TABLE 5 Subgroup analyses of effect of resveratrol on LDL

	No. of studies	MD	95% CI	I^2	Heterogeneity *P*	I^2 between groups	*P* for between-subgroup heterogeneity
Intervention dose						27.7%	0.24
≥1,000 mg/d	1	0.59	−0.66, 1.84	-	-		
<1,000 m/d	5	−0.21	−0.65, 0.24	87%	<0.00001		
Intervention time						0%	0.34
≥6 mo	2	−0.40	−1.41, 0.62	81%	0.02		
<6 mo	4	0.11	0.01, 0.20	0%	0.41		
BMI						92.9%	<0.00001
Normal (<25 kg/m^2)	1	−0.85	−1.19, −0.51	-	-		
Overweight (25–30 kg/m^2)	2	−0.07	−1.23, 1.09	53%	0.15		
Obesity (>30 kg/m^2)	3	0.11	0.01, 0.21	0%	0.80		
Lipid-lowering drugs						93%	<0.00001
Yes	4	0.10	0.01, 0.20	0%	0.50		
No	1	−0.85	−1.19, −0.51	-	-		
Not mentioned	1	0.59	−0.66, 1.84	-	-		

LDL, low-density lipoprotein; MD, mean difference.

TG is the predominant form of energy storage in mammals. AMP activated protein kinase (AMPK) and NAD-dependent protein deacetylase sirtuin-1 (SIRT1) are important factors in energy metabolism. Several studies have shown that resveratrol is an agonist of AMPK (30) and that activation of AMPK can inhibit sterol regulatory element–binding protein 1 activity, thereby preventing fatty acid synthesis (31). There is increasing evidence that SIRT1 regulates mitochondrial biogenesis, energy homeostasis, and insulin sensitivity (32). SIRT1 might also activate AMPK, thus reducing oxidative stress as evidenced by improved insulin sensitivity and blood glucose control (33).

SIRT1 also increases mitochondrial activity and fatty acid oxidation (32). When resveratrol was administered for 30 days at 150 mg/d, plasma resveratrol stabilized at an average level of 183 ng/mL and mimicked calorie-restricted health effects. In the absence of weight changes, resveratrol reduced the metabolic rate during sleep and rest and improved skeletal muscle mitochondrial function and lipid oxidative capacity (34).

There were still some limitations to this meta-analysis. First, of the 10 studies included, 3 involved male subjects only and 7 included male and female subjects. Thus, we could not perform subgroup analyses on the basis of gender, yet men and women may respond differently to resveratrol because women are more affected by hormone levels. Second, most of the studies did not report subject ethnicity. Thus, we could not perform subgroup analyses on the basis of ethnicity, yet there may be differences in the degree of blood lipid changes among different ethnic groups. Third, resveratrol dose and intervention time differed greatly between studies, from 8.1 to 3,000 mg/d and from 1 to 12 months, respectively. Because the number of studies that met the inclusion criteria was small, our subgroup analyses of these factors were relatively imprecise, with only two subgroups used per analysis (dose categories ≥ 1,000 and < 1,000 mg/d, intervention time categories ≥ 6 and < 6 months). Fourth, it is unclear whether other lipid-lowering drugs such as statins modify the effect of resveratrol on blood lipid levels. Two of the studies did not report whether lipid-lowering drugs were taken and thus could not be included in the relevant subgroup analyses. Finally, among the 10 eligible articles that met the inclusion criteria, the original data from 1 article could not be retrieved, which may have had led to a certain degree of bias.

Conclusion

Longer resveratrol interventions reduced TG levels in patients with type 2 diabetes, whereas resveratrol increased TC and LDL in patients with BMI within the obesity range. Also, resveratrol increased LDL in patients taking lipid-lowering drugs. Given the limitations of this meta-analysis, more high-quality RCTs are needed to confirm these results.O

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