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Resveratrol in diabetes mellitus and other metabolic conditions

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Abstract

Introduction and purpose

Resveratrol is a polyphenol with many properties, including activity against glycation, oxidative stress, inflammation, neurodegeneration, carcinogenesis and aging. It appears to be a promising compound for the prevention and treatment of metabolic diseases. The aim of this review is to summarize the results of the latest clinical trials that concern effects of resveratrol in diabetes mellitus type 1 and 2 and its complications - diabetic foot ulcers, diabetic nephropathy and non-alcoholic fatty liver disease.

A brief description of the state of knowledge

Based on in vitro studies and animal models, it has been observed that resveratrol reverses the factors causing premature death: obesity, hypertension, and hyperlipidemia. Because of its anti-inflammatory, antioxidant, cardioprotective and blood lowering glucose effects, it appears to be a promising compound for the treatment of metabolic conditions. The review presents different clinical trials concerning the efficiency of resveratrol supplementation in patients with diabetes mellitus and metabolic syndrome and their complications. Most studies focused on assessing the effect of resveratrol supplementation as an adjunctive treatment of diabetes mellitus type 2 and in this group of patients it gave the best results causing reduction of fasting glucose levels, fasting insulin concentration, insulin resistance and improvement of insulin sensitivity and lipid profiles.

Conclusions

Resveratrol remains a potential drug in the treatment of metabolic diseases like diabetes mellitus. However, the results of the conducted trials are inconscient. More research is needed to confirm the effectiveness of resveratrol supplementation in treating diabetes, its complications and other metabolic conditions.

Keywords: resveratrol; diabetes; metabolism

Introduction and purpose

Resveratrol is a polyphenolic compound produced by various plants in response to stress. The rich source of resveratrol are grapes, peanuts, mulberries and blueberries. Despite rapid absorption, it is characterized by low bioavailability and solubility [1]. It can present anti-inflammatory, antioxidant, antiplatelet, cardioprotective, blood glucose lowering, or even anti-cancer effects [2]. Due to the wide beneficial effect on the human body, the possibility of using resveratrol in common health problems is being searched for [3]. New drug delivery systems are being developed to increase the bioavailability of this potential drug [4].

Diabetes mellitus is a common disease that affected approximately 537 million adults worldwide in 2021 [5]. It is a chronic and yet challenging disease that leads to the occurrence of many serious complications, including peripheral neuropathies and atherosclerosis. New drugs in the treatment of diabetes are constantly searched [6].

Resveratrol appears to be a promising compound for the treatment and prevention of diabetes. The aim of this study is to review the latest research on the effects of resveratrol in diabetes mellitus type 1 and 2 and its complications - diabetic foot ulcers, diabetic nephropathy and non-alcoholic fatty liver disease.

Methods

The aim of this work is to review the potential use of resveratrol supplementation in patients with diabetes mellitus. The PubMed/MEDLINE database was used to identify potential articles for analysis using the following search terms: (diabetes) AND (resveratrol), with time frame 2010-2022. The literature search was conducted on August 30th 2022, and 1,255 items were obtained.

The results were filtered for the character of the studies (clinical trials, 49 results). The following types of studies were excluded: questionnaire-based surveys, meta-analyses and reviews. As the main focus of this review was to examine the influence of this substance on main parameters that are dysregulated in metabolic diseases, only studies that enrolled patients with diabetes mellitus and obesity were included.

As a result of the above searches, a total of 22 studies were included for review. All studies were randomized controlled trials.

Description of the state of knowledge

Diabetes mellitus type 1

A single-center study conducted by Movahed A. examined the efficacy and safety of resveratrol in patients with diabetes mellitus type 1. The study enrolled 13 patients at the age of 13 to 45 years old, treated with insulin. As it was reported, only 2 months of 500 mg resveratrol supplementation twice a day significantly lowered fasting glucose concentration and HbA1c. No significant changes in body weight, insulin concentration and insulin resistance were detected, nor hepatic and renal parameters [7].

Diabetes mellitus type 2

13 papers studied resveratrol impact on patients with DM 2 (Table 1.) [8-20]. Five studies detected a significant reduction in fasting glucose in patients that supplemented resveratrol for 4 to 24 weeks compared to those who did not [9,17-20]. Long term resveratrol supplementation significantly decreased insulin concentration [12,18-20] and improved insulin sensitivity [8,12,18,20]. Moreover, 3 studies reported a significant change in lipid profile, namely an increase in HDL-cholesterol levels and decrease in total cholesterol levels [9,18]. One study reported a significantly lowered LDL-cholesterol level after resveratrol supplementation [9].

Table 1. A review of studies regarding resveratrol supplementation in patients with diabetes mellitus type 2.

				Parameters			
Author, year	**Dose [mg/day]**	**No. of partici-pants**	**Time frame**	**Fasting glucose**	**Insulin concentration**	**Insulin resistance/sensitivity**	**Lipid profile**
Brasnyó, P.(2011) [8]	10	19	4 weeks	-	No difference	A significant reduction in insulin resistance	-
Bhatt, J.K.(2012) [9]	250	62	3 months	A significant reduction	-	-	A significant reduction in total cholesterol and LDL-cholesterol level. No significant changes in HDL and TG.
Tomé-Carneiro, J.(2013) [10]		35	12 months	No significant difference	-	-	No significant differences
Goh, K.P.(2014) [11]	3000	10	12 weeks	No significant differences	No significant differences	No significant differences in insulin resistance and insulin sensitivity	No significant differences
Zare Javid, A.(2016) [12]	480	43	4 weeks	No significant difference	A significant reduction	A significant reduction in insulin resistance	No significant differences
Thazhath, S.S.(2016) [13]	1000	14	5 weeks	No significant difference	-	-	-
Bo, S.(2016) [14]	500 or 40	192	6 month	No significant difference	No significant differences	No significant difference	No significant differences
Timmers, S.(2016) [15]	150	17	30 days	No significant difference	No significant difference	No significant difference	No significant differences
Imamura, H.(2017) [16]	100	50	12 weeks	No significant difference	-	-	No significant differences
Khodabandehloo, H.(2018) [17]	800	45	8 weeks	A significant reduction	-	-	-
Hoseini, A.(2019) [18]	500	56	4 weeks	A significant reduction	A significant reduction	A significant reduction in insulin resistance and a significant increase in insulin sensitivity	A significant increase in HDL-cholesterol levels and a significant reduction in the total cholesterol/HDL-cholesterol ratio
Abdollahi, S.(2019) [19]	1000	76	8 weeks	A significant reduction	A significant reduction	A close to being significant reduction in insulin resistance. No significant difference in insulin sensitivity.	A significant increase in HDL-C
Mahjabeen, W.(2022) [20]	200	110	24 weeks	A significant reduction	A significant reduction in fasting insulin	A significant reduction	No significant differences

Insulin sensitivity

Based on in vitro studies and animal models, it has been observed that resveratrol reverses the factors causing premature death: obesity, hypertension, and hyperlipidemia. The Morten M Poulsen study investigates the metabolic effects of high doses of reservetrol in obese people. In a randomized, double-blind study: 24 obese men (without other diseases) were divided into two groups and received: one resveratrol and the other placebo. Extensive metabolic tests (assessment of glucose turnover and insulin sensitivity) were performed before and after resveratrol treatment. Insulin sensitivity deteriorated slightly in both groups, and glucose turnover remained unchanged. Resveratrol also had no effect on blood pressure, resting energy expenditure or body fat content. The results differ from those observed in animal models, and are causing doubts on using resveratrol as a drug in metabolic disorders [21].

Another study performed by Miriam Méndez-del Villar et al. evaluated the effects of resveratrol on metabolic syndrome, insulin sensitivity and insulin secretion. Twenty four patients with metabolic syndrome were reported to the randomized, double blinded clinical trial. Half of the subjects received trans-resveratrol (500 mg) 3 times per day for 90 days, before meals, others received a placebo. Significant differences were observed in total body weight (94.4 ± 13.2 vs. 90.5 ± 12.3 kg), body mass index (BMI) (35.6 ± 3.2 vs. 34.3 ± 3.0 kg / m2), body fat mass (41.2 ± 7.9 vs 38.8 ± 6.0 kg) and waist circumference (WC) (109 ± 9 vs 105 ± 10 cm). There were also significant differences in the insulin AUC (48,418 ± 22,707 vs 26,473 ± 8,273 pmol / l) and the insulinogenic index (0.48 ± 0.22 vs 0.28 ± 0.08) [22].

Diabetic Foot Ulcers

One study regarded the influence of resveratrol on diabetic foot ulcers treatment. The study enrolled 48 patients with 1st and 2nd degree diabetic foot ulcers, measured in Wagener classification. Patients went under intervention which used collagen laminin-based dermal matrix conjuncted with resveratrol microparticles, achieving a reduction of time of treatment and general improvement compared with standard wound treatment procedures. Moreover, after one-month follow-up there were 57.82% wound closures in the resveratrol group and 26.63% in the group that received standard procedure [26]

Diabetic Nephropathy

In the United States and Europe, renal failure due to diabetic nephropathy has become the leading cause of end-stage renal disease [27]. One of the indicators of the development of diabetic nephropathy is albuminuria [28].

In a study by Sattarinezhad A. et al. resveratrol was introduced in 60 patients with type 2 diabetes and albuminuria. 500 mg/day of resveratrol was administered for 90 days. In addition, the patients were given losartan at a dose of 12.5 mg per day. There was a significant reduction in the urinary albumin/creatinine ratio compared with placebo. There was no reduction in eGFR and serum creatinine [29].

Non-alcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is one of the metabolic syndromes in the world. It can lead to liver cirrhosis and hepatocellular carcinoma. It is also the most common cause of liver transplantation. The causes of this disease are better known, but it is still difficult to find an effective therapy with no side effects.

A randomized, double blinded clinical trial in six obese male patients with NAFLD investigated the effect of resveratrol on basal and insulin-dependent very low-density lipoprotein triglycerides. Resveratrol was received at high doses- 300mg- three times a day for 6 months. In this study no positive effect of the drug on VLDL secretion, body weight and fat content in the liver were found [23].

Konstantinos Kantartzis et al. performed largest randomized, double blinded, clinical trial on 112 patients to explore resveratrol supplementation influence on liver fat content and cardiometabolic risk in overweight, obese and insulin-resistant subjects. After 12 weeks there was no significant reduction in liver fat in the resveratrol group. There was also no change in the assessment of cardiometabolic risk [24].

A study by Forouzan Faghihzadeh et al. assessed the effect of resveratrol supplementation on cardiovascular risk factors in patients with non-alcoholic fatty liver disease. The study was randomized, double-blinded and placebo-controlled. The group of fifty subjects received 500 mg of resveratrol or placebo for 12 weeks. Moreover, both groups were recommended to follow a balanced diet and implement physical activity. The results showed that drug supplementation significantly reduced alanine aminotransferase (ALT) and hepatic steatosis significantly more than placebo. No other significant effects were observed [25].

Conclusions

The increasing number of cases of diabetes contributes to the search for new methods of prevention or increasing the effectiveness of its treatment. So far, there have been few studies in the literature on the efficacy of resveratrol in the treatment of type 1 diabetes, and a single study has not shown significant treatment

outcomes. However, resveratrol supplementation appears to be effective in treating type 2 diabetes. Long term resveratrol supplementation significantly decreased insulin concentration.

Moreover, individual studies show that the additional use of resveratrol may have a significant impact on the improvement of the treatment of diabetes complications - diabetic foot ulcers or nephropathy. More research is needed to confirm the effectiveness of resveratrol supplementation in treating diabetes and its complications.

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