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ORIGINAL ARTICLE

Effect of Resveratrol Administration on Metabolic Syndrome, Insulin Sensitivity, and Insulin Secretion

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Abstract

Aim: This study evaluated the effect of resveratrol administration on metabolic syndrome, insulin sensitivity, and insulin secretion.
Methods: A randomized, double-blind, placebo-controlled clinical trial was carried out in 24 patients with diagnosis of metabolic syndrome in accordance with the International Diabetes Federation criteria. Glucose and insulin levels were measured after a 75-gram dextrose load. Triglycerides and high-density lipoprotein cholesterol concentrations at baseline were also evaluated. Twelve patients received *trans*-resveratrol (500 mg) three times per day before meals for 90 days. The remaining 12 patients received placebo at the same dose. The area under the curve (AUC) values of glucose and insulin, total insulin secretion, first-phase of insulin secretion, and insulin sensitivity were calculated.
Results: After resveratrol administration, there were significant differences in total weight (94.4 ± 13.2 vs. 90.5 ± 12.3 kg, $P = 0.007$), body mass index (BMI) (35.6 ± 3.2 vs. 34.3 ± 3.0 kg/m^2, $P = 0.006$), fat mass (41.2 ± 7.9 vs. 38.8 ± 6.0 kg, $P = 0.001$), and waist circumference (WC) (109 ± 9 vs. 105 ± 10 cm, $P = 0.004$). There were also significant differences in AUC of insulin ($48{,}418 \pm 22{,}707$ vs. $26{,}473 \pm 8{,}273$ pmol/L, $P = 0.003$) and insulinogenic index (0.48 ± 0.22 vs. 0.28 ± 0.08, $P = 0.004$).
Conclusions: Administration of resveratrol significantly decreases weight, BMI, fat mass, WC, AUC of insulin, and total insulin secretion.

Introduction

Metabolic syndrome is a highly prevalent disease worldwide and involves a group of endocrine disturbances such as obesity, impaired fasting glucose, dyslipidemia, and prehypertension. Metabolic syndrome increases the risk of developing atherosclerosis, cardiovascular diseases, and type 2 diabetes mellitus (T2DM) and is strongly associated with insulin resistance and the presence of compensatory hyperinsulinemia.[1,2]

Many organizations have established different diagnostic criteria and treatment algorithms for metabolic syndrome. In accordance with the International Diabetes Federation (IDF), the first line of treatment for metabolic syndrome involves lifestyle changes such as weight loss, changes in dietary composition, and an increment of physical activity.[3] In some cases, pharmacological intervention is indicated.

Resveratrol (3,5,4′-trihydroxystilbene) is a phytoalexin considered to be a natural polyphenol and is contained in grapes, red wine, and in some berries. It may exist in two isoforms, *cis* and *trans*, with *trans* being the most studied isoform and with the most pharmacological properties.[4] One of the properties of resveratrol is its antiobesity potential through different mechanisms, such as inhibition of the differentiation of preadipocytes to adipocytes, reduction of adipocyte proliferation, induction of adipocyte apoptosis, decrease of lipogenesis, increase in lipolysis, β-oxidation of fatty acid activity (which leads to a decrease of the inflammatory profile characteristic of obesity), diminution of lipid levels, and glucose homeostasis.[5]

The properties of resveratrol have been studied both in experimental models and in clinical trials in patients with obesity and T2DM. The results suggest that resveratrol may be an excellent therapeutic alternative for the prevention and treatment of metabolic syndrome; however, there is insufficient evidence from clinical trials that evaluates the effect of resveratrol on metabolic syndrome. The aim of this study was to evaluate the effect of resveratrol administration on metabolic syndrome, insulin secretion, and insulin sensitivity.

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Patients and Methods

A randomized, double-blind, placebo-controlled clinical trial was carried out in 24 patients between 30 and 50 years of age diagnosed with metabolic syndrome in accordance with IDF criteria,[3] without T2DM and previous pharmacological treatment for components of metabolic syndrome. Study subjects were selected from the same residential area and presented a similar socioeconomic status. No patient had morbid obesity, was excessively sedentary, or was engaged in heavy physical activity. All individuals were nonsmokers, and their body weight remained stable for at least 3 months prior to the study. There was no personal history of hepatic, renal, thyroid, or heart disease. During the 6 months prior to the study, patients did not use any drugs that could modify body weight, blood pressure, glucose, or lipid levels. Three days before tests, patients received an isocaloric diet containing a minimum of 250 grams of carbohydrates to ensure proper insulin secretion. Women were tested during the first phase of their menstrual cycle (days 3–8).

Patients were evaluated before and after the 3-month resveratrol or placebo intervention. All patients received medical/nutritional therapy and were instructed to continue with their normal physical activities. Tests were performed at 8:00 am after a 10- to 12-hr overnight fast. Height and body weight were measured with individuals wearing light clothes and without shoes. Height was measured with subjects standing, and the measurements were rounded to the nearest centimeter. Body weight was evaluated through a bioimpedance digital scale, and results were reported in kilograms with a decimal. Body mass index (BMI) was calculated by dividing body weight (kg) by height squared (m^2). Waist circumference (WC) was measured with a flexible tape at the midpoint between the lowest rib and the iliac crest and expressed in centimeters. Blood pressure was evaluated with a digital sphygmomanometer with the subject seated in a chair after a resting period of 5 min, on three occasions. The mean of the three measurements was considered as the value of systolic blood pressure (SBP) and diastolic blood pressure (DBP) expressed in mmHg. Blood samples were taken after the insertion of a catheter as an open route to facilitate the procedure and were taken at baseline and at 30, 60, 90, and 120 min after a 75-gram oral dextrose load. Blood was centrifuged at 2500 rpm, and serum was separated into two aliquots.The first was immediately analyzed to determine glucose and lipid profile, and the second aliquot was frozen at $-20°C$ for later insulin determinations.

Pharmacological administration

After randomization, 12 patients received *trans*-resveratrol capsules (500 mg) (Xi'an Xin Sheng Bio-Chem Co. Ltd.) three times per day before meals for 90 days. The remaining 12 patients received placebo at the same dose. Compliance was monitored with a personal diary and medication counting.

Laboratory measurements and calculations

Glucose, triglycerides (TGs), and total cholesterol levels were measured by enzymatic colorimetric methods with an automated analyzer with intra- and interassay coefficients of variation (CV) $<1\%$ and 2%, respectively, for all measurements. Insulin concentrations were measured with ion-exchange liquid chromatography with intra- and interassay CV of 4.6% and 5.9%, respectively. Fasting serum high-density lipoprotein cholesterol (HDL-C) levels were measured using an automated analyzer with intra- and interassay CV of 1.6% and 2.0%, respectively. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula as follows: LDL-C (mmol/L) = total cholesterol (mmol/L) − HDL-C (mmol/L) − [TGs (mmol/L)/2.2]. The area under the curve (AUC) of glucose and insulin was calculated with the polygonal formula. Total insulin secretion was calculated with the insulinogenic index (ΔABC insulin/ΔABC glucose). The first phase of insulin secretion was estimated using the Stumvoll index ($1283 + 1.829 \times$ insulin 30′ $- 138.7 \times$ glucose 30′ $+ 3.772 \times$ insulin 0′). Insulin sensitivity with Matsuda index [10,000/$\sqrt{}$glucose 0′ $\times$ insulin 0′) (mean glucose oral glucose tolerance test (OGTT) $\times$ mean insulin OGTT)].[6,7]

Statistical analyses

Sample size was calculated in accordance with a clinical trial formula[8] with a statistical confidence of 95%, statistical power of 80%, standard deviation (SD) for WC of 1.2 cm,[9] and expected between-group differences of at least 1.6 cm, obtaining a total of 12 patients per group including 20% of expected loss. For insulin secretion and insulin sensitivity, sample size calculation was lower. Values are expressed in accordance with the International System of Units (SI) and are presented as mean and SD. Nonparametric statistics were used. Intragroup differences were tested using the Wilcoxon signed-rank test and intergroup differences with Mann–Whitney U-test; $P \leq 0.05$ was considered significant.

Ethical considerations

The study was evaluated and approved by a local Ethics Committee, and written informed consent was obtained from all volunteers.

Results

There were no significant differences between groups at baseline. After 3 months of intervention, 21 patients completed the study, 11 from the resveratrol group and 10 from the placebo group. Of the 11 patients from the resveratrol group, 10 patients were female and one male. In the placebo group, five patients were male and five were female. The mean age of patients in the resveratrol group was 39.8 ± 5.4 years, whereas the mean age of patients in the placebo group was 40.3 ± 5.4 years.

After resveratrol administration there were significant differences in body weight, BMI, fat mass, and WC. There were also differences in AUC of insulin and insulin secretion (Table 1). There were no significant differences after placebo administration. No serious adverse events occurred during the study. Three patients did not complete the study due to early withdrawal.

Discussion

Metabolic syndrome increases the risk for cardiovascular disease and T2DM. Therapeutic lifestyle modification is the

Table 1. Characteristics Before and After the Interventions

	Placebo		*Resveratrol*	
	Baseline	*3 months*	*Baseline*	*3 months*
Body weight (kg)	91.0 ± 10.7	93.1 ± 9.1	94.4 ± 13.2	90.5 ± 12.3*
BMI (kg/m^2)	33.7 ± 3.7	34.0 ± 3.6	35.6 ± 3.2	34.3 ± 3.0*
Fat mass (kg)	36.1 ± 9.2	35.7 ± 9.1	41.2 ± 7.9	38.8 ± 6.0*
WC (cm)	104 ± 8	105 ± 7	109 ± 9	105 ± 10*
SBP (mmHg)	116 ± 13	121 ± 11	120 ± 13	116 ± 11
DBP (mmHg)	77 ± 8	78 ± 7	78 ± 8	78 ± 9
Glucose 0′ (mmol/L)	5.1 ± 0.4	4.5 ± 0.5	4.8 ± 0.6	4.6 ± 0.6
Glucose 30′ (mmol/L)	8.4 ± 1.1	7.6 ± 1.2	8.5 ± 1.8	7.9 ± 1.4
Glucose 60′ (mmol/L)	9.3 ± 1.8	8.0 ± 2.4	9.0 ± 2.7	8.5 ± 2.0
Glucose 90′ (mmol/L)	8.3 ± 2.3	7.3 ± 2.6	8.0 ± 1.8	8.2 ± 2.0
Glucose 120′ (mmol/L)	6.9 ± 2.2	6.3 ± 2.1	6.5 ± 1.7	6.5 ± 1.6
Cholesterol (mmol/L)	5.1 ± 0.9	5.4 ± 0.7	5.3 ± 0.8	5.3 ± 1.0
TGs (mmol/L)	2.6 ± 0.9	2.6 ± 1.7	2.8 ± 0.6	2.4 ± 0.7
HDL-C (mmol/L)	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.1	1.0 ± 0.1
LDL-C (mmol/L)	3.1 ± 1.2	3.3 ± 0.9	3.1 ± 0.8	3.2 ± 1.0
AUC glucose (mmol/L)	950 ± 167	848 ± 203	935 ± 188	904 ± 168
AUC insulin (pmol/L)	62955 ± 37620	54856 ± 31168	48418 ± 22707	26473 ± 8273*
Insulinogenic index	0.59 ± 0.29	0.60 ± 0.30	0.48 ± 0.22	0.28 ± 0.08*
Stumvoll index	1440 ± 619	1279 ± 599	1256 ± 601	1019 ± 335
Matsuda index	3.27 ± 1.5	4.72 ± 2.4	3.5 ± 1.5	4.2 ± 1.2

*$P < 0.01$ between baseline and 3 months within the resveratrol group.

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TGs, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AUC, area under the curve.

first-line therapy for these patients, but if this therapy fails or the risk of developing complications is high, drug therapy to modify each of the components of metabolic syndrome may be required.[10] No single pathogenic pathway has been identified as a valuable therapeutic target in metabolic syndrome; therefore, multiple drugs may be required for disease remission. Alternative medicine may be an option for treatment of all components of metabolic syndrome.[11] In our study, patients who received the natural polyphenol resveratrol had a statistical significant reduction of body weight, BMI, fat mass, and WC, with a clinical relevance for BMI only, decreasing from grade 2 to grade 1. Reduction of AUC of insulin and total insulin secretion were also found.

There is evidence showing that caloric restriction has an important effect on the life span of many species including primates and humans. Caloric restriction has been related with an increase of the activity and levels of sirtuins, a family of histone deacetylases, which have been implicated in metabolic processes and stress resistance, especially Sirt1 in mammals. The effects of Sirt1 appear to be beneficial because it triggers metabolic changes, similar to those observed in caloric restriction such as glucose homeostasis, control of insulin hypersecretion, lipid metabolism, fat mobilization, and adipokine secretion.[12–14] On the basis of the hypothesis that sirtuins are critical mediators of caloric restriction, many molecules have been studied to modify sirtuin activity. Resveratrol treatment leads to an increase of Sirt1 activity *in vivo* and in other species, such as rodents and primates, supporting the idea that resveratrol mimics a striking number of changes induced by dietary restriction.[15]

Our findings of the effect of resveratrol on body weight, fat mass, BMI, and WC could be explained by several pathways, such as, the modulation of the fat regulator peroxisome proliferator-activated receptor-γ (PPARγ) and genes mediating fat storage. Resveratrol also increases adenosine monophosphate (AMP)-activated protein kinase (AMPK) and PPARγ coactivator 1α (PGC-1α) activity, increases mitochondrial number, and improves motor function, demonstrating by these pathways that resveratrol opposes the effects of a high-calorie diet, improving health in mammals.[16] Other mechanisms may be an increase in lipolysis and induction of adipocyte apoptosis by the regulation of transcription factors and enzymes.[17–19] Despite this evidence, few clinical trials have evaluated the effect of resveratrol in patients with obesity. On a crossover, randomized, double-blind clinical trial carried out with 11 healthy obese males, administration of placebo or resveratrol (150 mg/day) reduced the sleeping and resting metabolic rate as well as increasing the activation of AMPK, Sirt1, and PGC-1α protein levels. However, the study did not find any differences in body weight or fat mass in contrast to the present study, probably due to the short time of administration and the lower dose.[20] Another clinical trial was carried out in 24 obese but otherwise healthy males who were administered resveratrol or placebo at a dose of 500 mg three times per day for 4 weeks. After resveratrol administration there were no effects on any of the evaluated biomarkers, which can be explained by the short duration of resveratrol administration, as seen in some studies that indicate that the bioavailability of this polyphenol is very low and therefore needs to accumulate in the tissues to exert an effect.[21]

In the present study, no significant differences were found in the lipid profile. There is evidence showing that resveratrol, through the AMP-activated AMPK pathway could regulate enzymes such acetyl-CoA carboxylase, reducing fatty acid synthesis, and inhibition of the 3-hydroxymethylglutaryl-CoA reductase (HMGCoA reductase), leading to a decrease in hepatic cholesterol synthesis.[22] Although the reduction of

TGs after resveratrol administration was not statistically significant, a reduction of 44 mg/dL is clinically important, a result consistent with other studies.[20]

Blood pressure did not show a significant reduction in the present study in opposition to other trials. The trial carried out in 11 healthy obese males had at baseline a mean SBP of 132 ± 3 mmHg, whereas subjects in the present study had a mean SBP at baseline of 120 ± 13. This may explain why the present study did not find significant differences. Subjects in the present study could be considered as normotensive at baseline, unlike subjects of the other trial who might be considered as prehypertensive.[20]

The effects of resveratrol on glucose metabolism are related to modifications of insulin secretion, glucose uptake, glycogen synthesis, diminution of adipose tissue, and glucagon-like peptide-1 (GLP-1) release by different mechanisms, such as increased expression of Sirt1 gene and protein. These are independent of changes in body weight, food intake, and circulating leptin levels. Resveratrol administration has also been related with decrease of insulin release in pancreatic islets by the diminution of glucose oxidation and reduction of glucose-induced hyperpolarization of the inner mitochondrial membrane, which leads to a reduction in the respiratory chain. Therefore, there is a decrease in adenosine triphosphate (ATP) levels and attenuated secretion of insulin and increased action of the insulin-dependent glucose transporter GLUT4.[13,23,24] In the present study, a significant decrease of AUC of insulin and total insulin secretion was found, an important issue in patients with metabolic syndrome due to the characteristic hyperinsulinemia that could lead to the development of T2DM. The present study did not find any significant differences in fasting glucose, postprandial glucose levels, AUC of glucose, or first phase of insulin secretion.

A trend was found in increasing insulin sensitivity. These findings are consistent with a recent meta-analysis that evaluated 11 randomized controlled trials in diabetic and nondiabetic subjects treated with resveratrol. The meta-analysis concluded that resveratrol significantly improves glucose control and insulin sensitivity in subjects with diabetes but does not affect glycemic measurements in non-diabetic subjects.[25]

This trial may be considered important for several reasons. First, the high incidence of metabolic syndrome and T2DM needs to be halted using a variety of preventive and therapeutic modalities. Second, there is sufficient evidence showing that administration of resveratrol through different mechanisms leads to control of obesity and various metabolic disorders. Third, resveratrol is a molecule that is already available as a nutritional supplement. Long-term studies with larger sample sizes and homogeneous populations will be necessary to confirm our findings and to recommend resveratrol as a treatment for metabolic syndrome.

In conclusion, our data suggest that resveratrol administration leads to a loss of body weight, especially fat mass and WC. It decreases the characteristic hyperinsulinemia of metabolic syndrome.

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Author Disclosure Statement

No conflict of interest is reported with regard to this manuscript. The authors declare no competing interests with the mentioned pharmaceutical company.

References

1. González-Ortiz M, Martínez-Abundis E, Jacques-Camarena O, et al. Prevalence of metabolic syndrome in adults with excess of adiposity: Comparison of the Adult Treatment Panel III criteria with the International Diabetes Federation definition. *Acta Diabetol* 2006;43:84–86.
2. Pineda CA. Síndrome metabólico: Definición, historia, criterios. *Colomb Med* 2008;39:96–106.
3. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. 1st International Congress of Prediabetes and the Metabolic Syndrome: Epidemiology, management and prevention of diabetes and cardiovascular disease, April 24, 2009, Berlin, Germany.
4. Catalog B, Batriel S, Taga Y, et al. Resveratrol: French paradox revisited. *Front Pharmacol* 2012;3:1–18.
5. Wang S, Moustaid-Moussa N, Chen L, et al. Novel insights of dietary polyphenols and obesity. *J Nutr Biochem* 2014; 25:1–18.
6. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: Comparison with the euglycemic insulin clamp. *Diabetes Care* 1999;22: 1462–1470.
7. Stumvoll M, Mitrakou A, Pimienta W, et al. Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. *Diabetes Care* 2000;23:295–301.
8. Jeyaseelan L, Rao PSS. Methods of determining sample sizes in clinical trials. *Indian J Pediatr* 1989;26:115–121.
9. Ramírez-Vargas E, Arnaud-Viñas MR, Delisle H. Prevalence of the metabolic syndrome and associated lifestyles in adult males from Oaxaca, Mexico. *Salud Publica Mex* 2007;49:94–102.
10. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005;365:1415–1428.
11. Affuso F, Mercurio V, Ruvolo A, et al. A nutraceutical combination improves insulin sensitivity in patients with metabolic syndrome. *World J Cardiol* 2012;26:77–83.
12. Allard JS, Perez E, Zou S, et al. Dietary activators of Sirt1. *Mol Cell Endocrinol* 2009;299:58–63.
13. De Kreutzenberg SV, Ceolotto G, Papparella I, et al. Downregulation of the longevity-associated protein sirtuin 1 in insulin resistance and metabolic syndrome: Potential biochemical mechanisms. *Diabetes* 2010;59:1006–1015.
14. Picard F, Kurtev M, Chung N, et al. Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma. *Nature* 2004;429:771–776.
15. Baur JA. Resveratrol, sirtuins, and the promise of a DR mimetic. *Mech Ageing Dev* 2010;131:261–269.
16. Baur JA, Pearson JK, Price NL, et al. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature* 2006;444:337–342.
17. Beaudeux JL, Nivet-Antonie V, Giral P. Resveratrol: A relevant pharmacological approach for the treatment of metabolic syndrome? *Curr Opin Clin Nutr Metab Care* 2010;6:729–736.
18. Fischer-Posovsky P, Kikulus V, Tews D, et al. Resveratrol regulates human adipocyte number and function in a Sirt1-dependent manner. *Am J Clin Nutr* 2010;92:5–15.

19. Timers S, Konings E, Bilet L, et al. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. *Cell Metab* 2011;14:612–622.
20. Poulsen MM, Vestergaard PF, Clasen BF, et al. High-dose resveratrol supplementation in obese men: An investigator-initiated, randomized, placebo-controlled clinical trial of substrate metabolism, insulin sensitivity, and body composition. *Diabetes* 2013;62:1186–1195.
21. Um JH, Park SJ, Kang H, et al. AMP-activated protein kinase-deficient mice are resistant to the metabolic effects of resveratrol. *Diabetes* 2010;59:554–563.
22. Skrobuk P, von Kraemer S, Semenova MM, et al. Acute exposure to resveratrol inhibits AMPK activity in human skeletal muscle cells. *Diabetologia* 2012;55:3051–3060.
23. Szkudelski T. Resveratrol-induced inhibition of insulin secretion from rat pancreatic islets: Evidence for pivotal role of metabolic disturbances. *Am J Physiol Endocrinol Metab* 2007;293:E901–E907.
24. Szkudelski T, Szkudelska K. Anti-diabetic effects of resveratrol. *Ann NY Acad Sci* 2011;1215:34–39.
25. Liu K, Zhou R, Wang B, et al. Effect of resveratrol on glucose control and insulin sensitivity: A meta-analysis of 11 randomized controlled trials. *Am J Clin Nutr* 2014;99:1510–1519.

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