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Oral resveratrol supplementation improves Metabolic Syndrome features in obese patients submitted to a lifestyle-changing program

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ABSTRACT

Aims: The aim of the present study was to evaluate the oral resveratrol effects associated with diet and physical training changes on anthropometric and biochemical parameters.
Main methods: 25 individuals aged from 30 to 60 years old; with Body Mass Index (BMI) ≥ 30 kg/m^2 were included in the study. Following the primary evaluation (anthropometric and clinical), the patients were randomly divided into 2 groups: (1) Placebo: Physical activity program + Diet + Placebo; (2) Resveratrol: Physical activity program + Diet + Resveratrol (RVS) (250 mg/day) for three months. Anthropometric and biochemical parameters were evaluated at baseline and after the treatment period.
Key findings: The main findings showed that the resveratrol supplementation improved total cholesterol (TC), High-density Lipoprotein cholesterol (HDL-c), Very-low density Lipoprotein cholesterol (VLDL-c), urea, creatinine and albumin serum levels.
Significance: These findings indicate that this polyphenol may be an option to potentiate the beneficial effects induced by dietary and physical activity programs in the Metabolic Syndrome (MetS) treatment.

1. Introduction

The Metabolic Syndrome (MetS) prevalence is increasing significantly and is considered a serious health problem worldwide [1]. The inadequate management of obesity and its complications comprise one of the main contributing factors for this increasing prevalence [1–3]. MetS is mainly characterized by a cluster of cardiovascular risk factors including hypertension, hyperglycemia, hypertriglyceridemia, central obesity (measured by waist circumference -WC) and insulin resistance [4,5]. Central obesity, assessed via waist circumference is a widely recognized cardiovascular risk predictor reflecting the visceral adiposity deposition [6–8]. However, some other parameters are also related to MetS, such as non-alcoholic fat liver disease, which seeks further studies aiming to determine the complications risks [1,4,9–11].

The primary MetS control is a contemporaneous world challenge [12], being the inadequate dietary pattern [13], physical inactivity [14] and genetic predisposition [15] among the main contributing factors for the MetS development. Up to date, there is no exclusive treatment for this syndrome [10]. Considering that preventive measures usually fail, and the therapeutic options are insufficient, new treatment approaches are being investigated [2].

It is known that a lifestyle change, focusing on a diet quality improvement and physical activity are the first MetS treatment option [16], being the weight loss the key element for the improvement of all MetS aspects [17,18]. The nutraceutical therapies, which include resveratrol, have demonstrated beneficial effects on the anthropometric and cardiometabolic risk factors, and may be considered a possible treatment option [10,19–22]. Considering that resveratrol is metabolized by the intestinal microbiota and modulates its composition, the interaction of this polyphenol and the host microbiome may strongly influence the MetS treatment efficiency, increasing bioavailability, inducing the production of certain metabolites or even promoting some specific bacteria growth [22–25]. Therefore, the interaction resveratrol/microbiota might be a key-element in the MetS treatment.

The chemical compound, resveratrol (3,5,4-trihydroxystilbene) (RSV) is a polyphenol described in 1940, when it was isolated for the first time from hellebore white roots. Years later, it was extracted from the plant *Polygonum cuspidatum*, which is widely used on the Chinese

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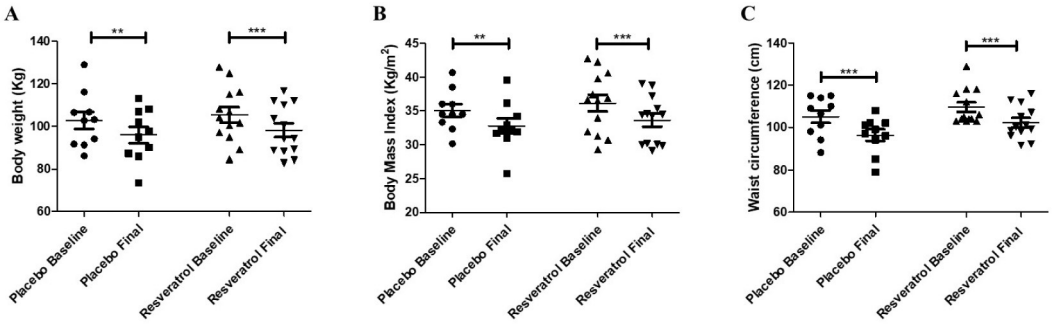

Fig. 1. Anthropometric parameters of individuals before and after treatment with placebo or resveratrol. A) Body Weight (Kg); B) Body Mass Index (Kg/m^2); C) Waist circumference (cm). Sample size: Placebo n = 12, and Resveratrol n = 13. *p > 0.05; **p > 0.01; ***p > 0.001.

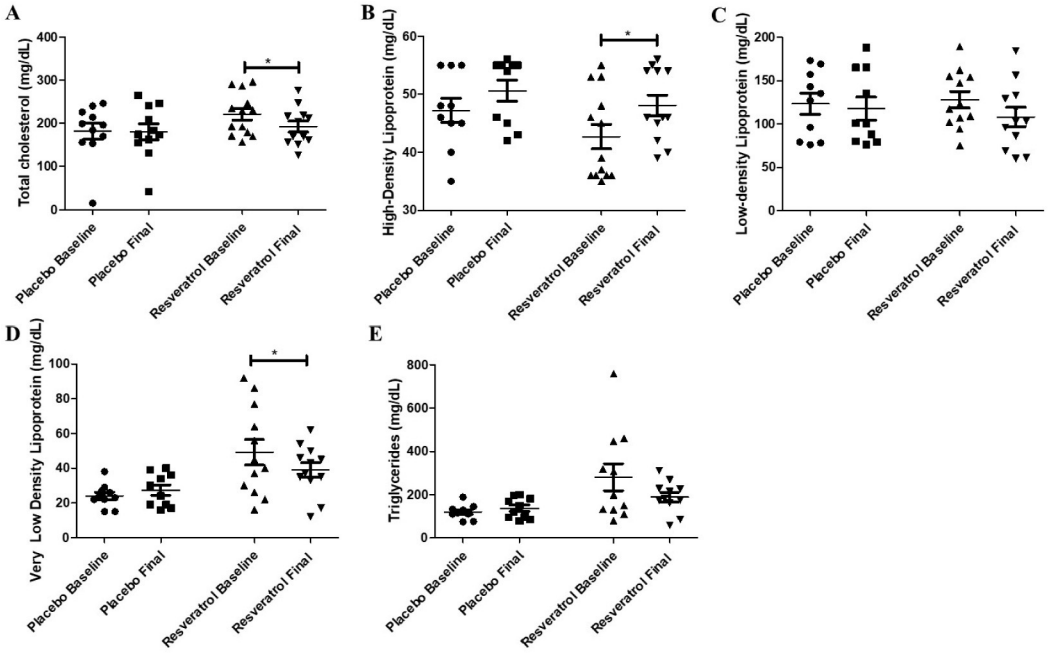

Fig. 2. Lipid profile of individuals before and after treatment with placebo or resveratrol. A) Total cholesterol (mg/dL); b) High-density Lipoprotein (mg/dL); C) Low-density Lipoprotein (mg/dL); D) Very Low Density Lipoprotein (mg/dL); Triglycerides (mg/dL). Sample size: Placebo n = 12, and Resveratrol n = 13. *p > 0.05; **p > 0.01; ***p > 0.001.

Traditional Medicine [26]. It is known that resveratrol can be found in different amounts in more than seventy plants, and is also present in beverages and foods such as blackberries, peanuts, grapes and their derivatives (e.g.) red wine [27]. In the plants metabolism, the resveratrol acts as a phytoalexin, a toxic compound produced as a defense mechanism in response to the presence of pests and other stressful situations like climate.

Resveratrol oral treatment seems to modulate metabolism in different tissues, however, there is no evidence on the existence of specific receptors, especially associated with its absorption and pharmacokinetics [28], however it is currently clear that resveratrol is able to activate sirtuins (Sirt) enzymes. Most of the resveratrol studies reports cardioprotective effects, although there are also evidences regarding other pharmacological therapies in several chronic diseases, such as cancer, Type 2 Diabetes (T2D) and Alzheimer's disease, besides its antithrombotic, anti-osteoporotic and antimicrobial properties [10,27,29]. It is well established, as for other polyphenols, that resveratrol acts through different mechanisms. This compound presents an important antioxidant activity and interacts with different receptors, kinases and enzymes [30,31].

In this perspective, the aim of the present study was to evaluate the oral resveratrol beneficial effects modulating biochemical, and clinical parameters after professional orientation for lifestyle changes associated with physical activity and diet regulation in the MetS patient's treatment.

2. Subjects and methods

2.1. Study population and study design

The study was performed by the Medical and Nutrition Services/Tancredo Neves Ambulatory Specialties Center - CAETAN/Universidade Estadual de Montes Claros-UNIMONTES with volunteers linked to the Police Offices Corporations (Montes Claros, MG), including current Police Offices and some of their relatives. This study was reviewed and approved by the Human Ethics Committee from the Universidade Estadual de Montes Claros (n° CAAE 01987912.0.0000.5146). Informed consent was obtained from all included participants.

The participants were women and men aged between 30 and 60 years. The exclusion criteria were set as follows: pregnant women, individuals submitted to bariatric surgery, under use of anorexigenic drugs, and/or with Body Mass Index (BMI) < 30 kg/m^2.

Patients with contraindications for physical activity due to skeletal-

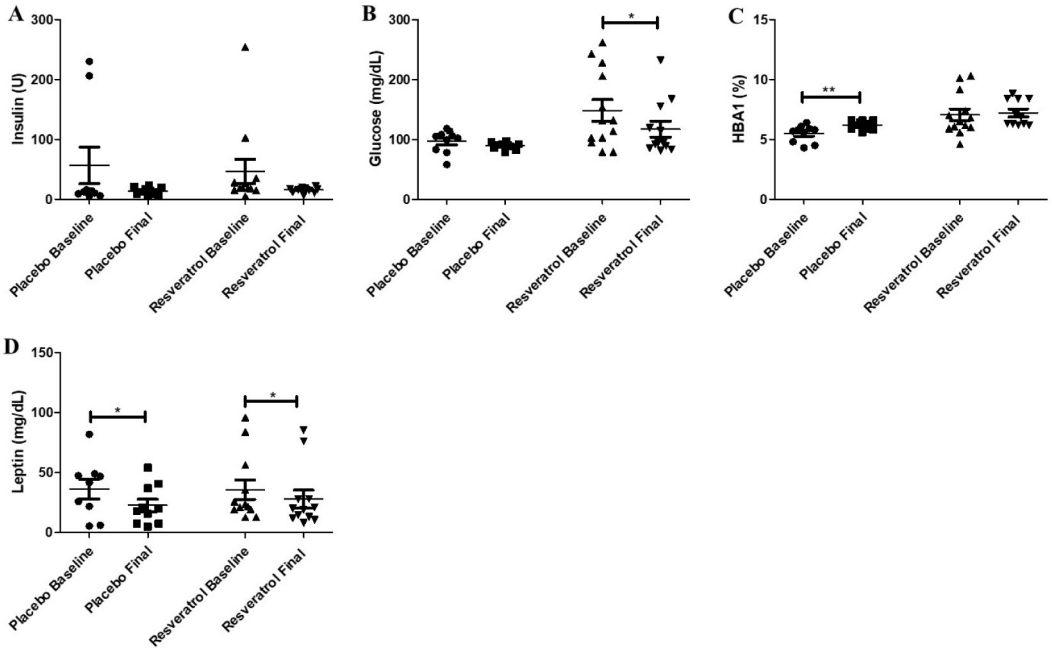

Fig. 3. Energetic and glycemic metabolic parameters of individuals before and after treatment with placebo or resveratrol. A) Insulin (U); B) Glucose (mg/dL); Glycated Hemoglobin (HBA1) (%); Leptin (mg/dL). Sample size: Placebo n = 12, and Resveratrol n = 13. *p > 0.05; **p > 0.01; ***p > 0.001.

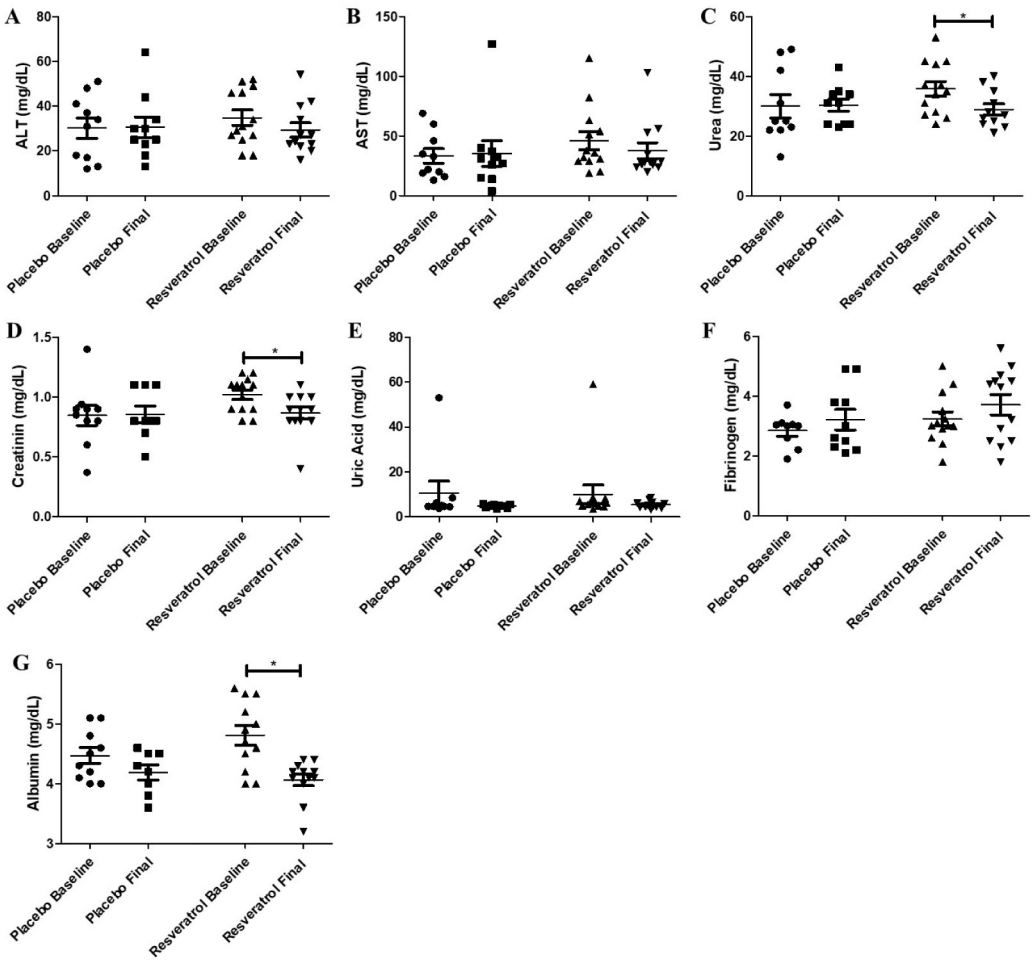

Fig. 4. Biochemical parameters of individuals before and after treatment with placebo or resveratrol. A) Aspartate aminotransferase (ALT) (mg/dL); B) Alanine aminotransferase (AST); C) Urea (mg/dL); D) Creatinine (mg/dL); D) Uric Acid (mg/dL); F) Fibrinogen (mg/dL); G) Albumin (mg/dL). Sample size: Placebo n = 12, and Resveratrol n = 13. *p > 0.05; **p > 0.01; ***p > 0.001.

Table 1
Individuals baseline anthropometric and biochemical parameters.

Variables	Placebo (n = 09)	Resveratrol (n = 13)	p-Value
Body weight	102.71 ± 12.97	105.39 ± 13.04	0.629
BMI	35.03 ± 3.00	36.14 ± 4.49	0.507
WC	105.05 ± 9.42	109.62 ± 8.28	0.231
TC	198.40 ± 33.13	221.00 ± 48.55	0.221
LDL-c	123.30 ± 38.34	127.83 ± 33.34	0.770
HDL-c	47.20 ± 6.62	42.69 ± 7.59	0.151
VLDL-c	24.10 ± 6.70	49.25 ± 25.63	**0.006**[a]
Triglycerides	120.40 ± 33.10	294.92 ± 191.81	**0.007**[a]
Insulin	56.67 ± 91.72	46.57 ± 69.91	0.777
Glycemia	87.10 ± 9.13	138.77 ± 66.29	**0.024**[a]
HBA1C	5.49 ± 0.70	7.05 ± 1.76	**0.010**[a]
Vitamin D	26.80 ± 3.40	29.44 ± 4.55	0.141
Leptin	36.30 ± 24.16	35.76 ± 27.98	0.964
UricAcid	10.58 ± 15.96	10.05 ± 14.77	0.937
AST	30.20 ± 14.44	34.85 ± 12.39	0.416
ALT	33.30 ± 19.35	46.08 ± 27.39	0.223
Fibrinogen	2.84 ± 0.54	3.23 ± 8.86	0.240
Urea	30.00 ± 12.23	35.85 ± 8.83	0.197
Creatinine	0.85 ± 0.26	1.02 ± 0.14	0.055
Albumin	4.47 ± 0.42	4.81 ± 0.57	0.137

BMI: Body Mass Index; WC: Waist Circumference; LDL-c: Low-density lipoprotein cholesterol; HDL-c: High-density lipoprotein cholesterol; VLDL-c: Very low-density lipoprotein cholesterol; HBA1C: Hemoglobin A1c; AST: alanine aminotransferase; ALT: aspartate aminotransferase. Baseline – Placebo and Resveratrol. Student's *t* test was applied.

[a] Mann-Whitney test was applied for the variables without normal distribution.

muscle, neurological, vascular, pulmonary and/or cardiac problems; those under hypolipidemic, antidepressant and/or anticoagulant medications; People with psychiatric disorder; Diagnosed hypothyroidism; Pregnant patients; And those who were difficult to contact and/or were lost to follow up were excluded. A total of 25 individuals were eligible for the study. All patients received information regarding the study through the informed consent.

Following the primary evaluation, the patients were randomly divided into 2 groups: (1) **Placebo**: Physical activity program + Diet + Placebo; (2) **Resveratrol**: Physical activity program + Diet + RVS (250 mg/day) (n = 13). The randomization was set by draw. Both groups were treated for three months, and the physical activity program was performed 3 times a week. The resveratrol dose was based on previously published studies [32,33].

This is a study with evaluations at baseline, and four subsequent monthly evaluations (time 0 (T0) to time 3 (T3)), comprising 12 weeks of dietary intervention based on nutritional counseling, and physical activity. It was considered abandonment (non-adherence to the nutritional intervention or physical activity programs), when the patient did not return to the time 2 (T2) and/or T3 follow-ups, as these points were important for the biochemical parameters evaluation, stopped following the physical activity plan, and/or using the resveratrol/placebo.

The following characteristics were evaluated at baseline, and after the treatment period: Anthropometric parameters: Body weight, body mass index and waist circumference. Biochemical and clinical parameters: Insulin, fasting glucose, hemoglobin A1C (HBA1C), leptin, uric acid, fibrinogen, urea, creatinine, albumin, total cholesterol (TC), Low-density Lipoprotein cholesterol (LDL-c), High-density Lipoprotein cholesterol (HDL-c), Very-low density Lipoprotein cholesterol (VLDL-c), triglycerides (TG), alanine aminotransferase (AST) and aspartate aminotransferase (ALT). Biochemical and anthropometric data, and dietary intake were assessed at baseline and T3.

2.2. Nutritional assessment and dietary intervention

The initial evaluation consisted on a consult with nutritionist, which lasted approximately 60 min, where individualized dietary plans were given. For the dietary history, performed at baseline and T3, two 24-hour dietary recall forms [32,34,35] were applied (in two different days, 1 chosen between Monday to Friday and 1 between Saturday and Sunday) to evaluate food intake, identifying the meal times and frequencies, eating habits and possible intolerances and/or allergies.

The participant's diagnosis was used for the nutritional therapy establishment. The nutritional diagnosis was based on the clinical diagnosis, dietary history evaluation, metabolic, and anthropometric parameters. At this point, total calorie value (TCV) consistent with the obtainment and\or maintenance of the healthy body weight was provided.

The prediction was to lose 5% to 10% of the initial body weight [36], through hypocaloric diets (reductions of 500Kcal or more of the estimated energy requirement (EER) predicted or obtained from dietary

Table 2
Anthropometric and biochemical parameters of individuals treated with placebo or resveratrol, before and after the 12 weeks of intervention.

Variables	Placebo (n = 09)			Resveratrol (n = 13)		
	Before	After	p-Value	Before	After	p-Value
Bodyweight	102.7 ± 12.9	95.9 ± 12.1	**0.006**	105.4 ± 13.0	98.1 ± 11.7	**0.000**
BMI	35.0 ± 3.0	32.8 ± 3.6	**0.003**	36.1 ± 4.5	33.6 ± 3.5	**0.000**
WC	105.0 ± 9.4	96.3 ± 8.6	**0.001**	109.6 ± 8.3	102.2 ± 7.8	**0.000**
TC	198.4 ± 33.1	193.7 ± 44.1	0.568	221.0 ± 48.6	192.1 ± 43.9	**0.031**
LDL-c	123.3 ± 38.3	117.7 ± 42.0	0.483	127.8 ± 33.3	108.1 ± 38.1	0.241
HDL-c	47.2 ± 6.6	50.6 ± 5.8	0.253	42.7 ± 7.6	48.1 ± 6.2	**0.026**
VLDL-c	24.1 ± 6.7	27.4 ± 9.5	0.209	49.3 ± 25.6	39.1 ± 14.3	**0.025**
Triglycerides	120.4 ± 33.1	137.1 ± 47.4	0.203	294.9 ± 191.8	189.9 ± 73.2	0.094
Insulin	56.7 ± 91.7	13.9 ± 6.1	0.194	46.6 ± 69.9	15.6 ± 4.1	0.154
Glycemia	87.1 ± 9.1	89.4 ± 5.7	0.363	138.8 ± 66.3	117.1 ± 45.9	0.116
HBA1C	5.5 ± 0.7	6.2 ± 0.4	**0.005**	11.3 ± 15.0	11.7 ± 15.6	0.343
Leptin	36.3 ± 24.2	22.7 ± 16.2	**0.031**	35.8 ± 27.9	28.0 ± 25.5	**0.014**
Uric acid	10.6 ± 15.9	4.8 ± 0.7	0.345	10.1 ± 14.8	5.4 ± 1.6	0.302
ALT	30.2 ± 14.4	30.6 ± 14.5	0.948	34.9 ± 12.4	29.3 ± 11.0	0.099
AST	33.3 ± 19.4	35.3 ± 34.1	0.874	46.1 ± 27.4	37.7 ± 23.5	0.440
Fibrinogen	97.0 ± 136.9	5.1 ± 5.7	0.535	82.1 ± 151.9	3.7 ± 1.2	0.199
Urea	30.0 ± 12.2	30.3 ± 6.5	0.933	35.9 ± 8.8	28.9 ± 6.3	**0.046**
Creatinine	0.9 ± 0.3	1.6 ± 2.3	0.344	1.0 ± 0.1	0.9 ± 0.2	**0.021**
Albumin	4.5 ± 0.4	7.8 ± 11.3	0.371	4.8 ± 0.6	4.0 ± 0.4	**0.000**

BMI: Body Mass Index, WC: Waist Circumference, LDL: Low-density lipoprotein, HDL: High-density Lipoprotein; VLDL: Very-low density lipoprotein, HBA1C: glycated hemoglobin, AST: aspartate transaminase, ALT: alanine transaminase. T-test was applied to verify differences before and after intervention.
Bold = P Value under 0,05

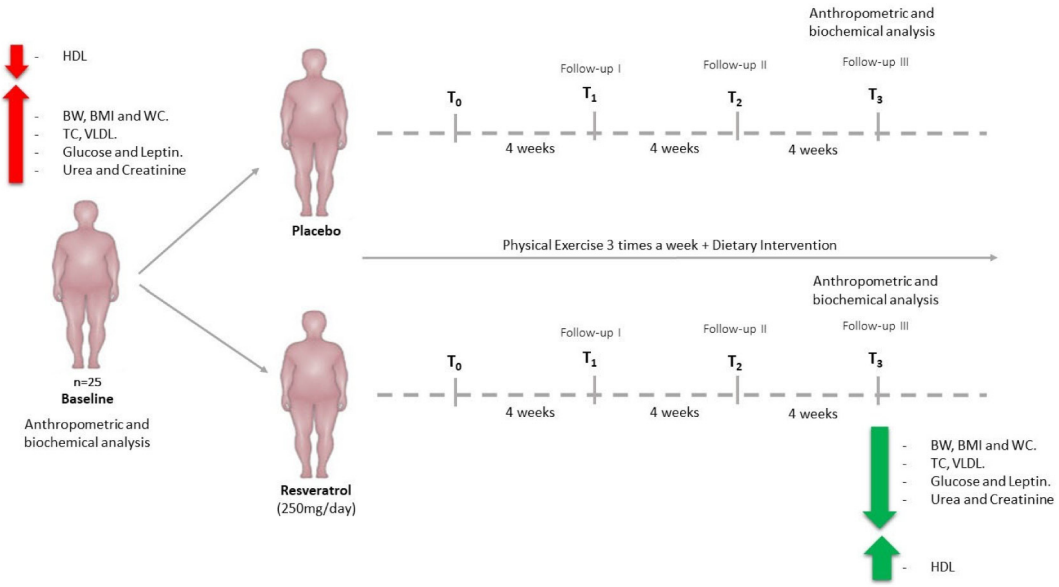

Fig. 5. Study design and main findings summary. BMI: Body Mass Index, WC: Waist Circumference, HDL: High-density Lipoprotein; VLDL: Very-low density lipoprotein, TC: Total Cholesterol.

history). The EER was calculated considering from 20 to 25 kcal/kg current weight\day aiming to promote 0.5 kg/week ponderal losses [36,37].

Information regarding nutritional education were given to the participants, and the details on the Mediterranean-based dietary plan, were provided [38]. Diets rich vegetables, fruits (5 portions/day), whole grains, virgin olive oil, lean meats, read meat (< 2 times a week), oilseeds (1 Brazil nuts and 3 walnuts/day), water (> 2 l/day), low fat dairy and foods rich in magnesium, potassium, calcium, fiber, antioxidant and polyphenol-rich teas (approximately 2 cups/day) (yerba mate: phenolic acids, caffeoyl derivatives such as chlorogenic acid (GCA) and some flavonoids such as rutin, quercetin, kaempferol and luteolin, and green tea: catechin, epicatechin, epicatechin 3-gallate) [39], were prescribed. Furthermore, the importance of breakfast consumption was emphasized [34,40]. All prescribed diets were calculated, with the support of the software "Programa de Apoio à Nutrição – Version 2.5 Dis/UNIFESP – Escola Paulista de Medicina".

Moreover, for the participants who consumed alcohol, a 30 g ethanol/day for men and 15 g ethanol/day for women were recommended. The participants were also questioned about other lifestyle habits, such as the habit of smoking, and were encouraged to adopt better lifestyles.

In the follow-ups, the participant's informed quantitatively and qualitatively their dietary history, thus, allowing the nutritionist to evaluate adherence or not to the initially proposed dietary plan. Each follow-up session lasted approximately 40 min.

2.3. Physical training and lifestyle program

The physical activity was measured by the total time of exercise performed during the week. According to this measurement, the participants were classified as: active (when they practice 150 min or more per week) and insufficient active (when they practice < 150 min) [41]. All the participants were encouraged to adopt a physical activity plan with the responsible physician consent. A physical educator, taking into account the participant's physical aptitude, individually proposed the physical activity plan. In general, all participants were prescribed 180 min/week of exercise (resistance/force, and running or bicycle).

The physical activity prescription was based on the guidelines established for cardiovascular health in the general population. The prescription was individualized in order to maximize the training benefits, taking into consideration each participant's physical aptitude. The participants were encouraged to perform every week from 150 to 200 min of moderate physical activity, or from 75 to 150 min of aerobic physical activity of vigorous intensity or an equivalent combination of moderate/vigorous intensity aerobic activity. The participants were also stimulated, respecting their individual physical limitations, to perform muscle strength activities 2 to 3 times a week.

2.4. Anthropometric measurements

Body weight was measured in kilograms (kg) in an electronic scale Balmak, Model BK-50FA (minimum capacity of 1 kg and a maximum of 150 kg, sensitivity of 50 g and calibrated by the Institute of Weights and Measures) with the participants in typical indoor clothing without shoes. The height (m) was determined to the nearest 0.1 cm, with the participants standing upright against an aluminum stadiometer (Model BK-50FA), coupled to the scale (maximum capacity of 200 cm, with intervals of 0.5 cm, without shoes. Body Mass Index was used for the overall nutritional status, according to the World Health Organization [42]. Having said that, in this study the participants were classified in the following groups: overweight: BMI ≥ 25 and < 30 kg/m^2 and obese as BMI ≥ 30 kg/m^2 [43].

For the Waist Circumference assessment, an inelastic tape was used, with a scale of 0.5 cm placed without pressure at the smallest circumference between the bottom of the last rib and the iliac crest [44–46]. For females, WC ≥ 80 cm and males ≥94 was classified as increased, WC ≥ 88 cm for females and 102 for males are classified as very increased [45].

2.5. Biochemical measurements

Before and after the treatment period, biochemical parameters were also assessed. The participants were asked to suspend the physical activity practice in the previous day of the exam, and fast for 12 h. Blood was collected via peripheral venipuncture.

Serum was obtained after centrifugation (600 ×g for 10 min at 4 °C). Specific enzymatic Elisa Kits (DSA BioELISA, USA) were used for the assessment of serum levels of fasting glucose [47], TC, HDL-c, LDL-c, VLDL-c, and triglycerides (TG) [48,49].

The levels of glucose, HBA1C, Leptin, Uric Acid, Alanine Aminotransferase (ALT), Aspartate Transaminase (AST), Fibrinogen,

Urea, Creatinine, Albumin were assessed.

2.6. Statistical analysis

Data is described as mean ± standard deviation to compare both groups (Placebo vs. RSV). Students' t for independent samples was applied to compare differences at baseline and before/after treatment in both groups (placebo and resveratrol), and Mann-Whitney test was applied for the variables without normal distribution. Statistical significance was set as $p < 0.05$. In order to better visualize the mean values from each treatment times and groups, a table was designed (Table 2), and to better visualize the differences among time and groups, graphs were designed (Figs. 1–4). Sample calculation was not performed as it is a feasibility study. The results presented in the tables were analyzed using Predictive Analytics Software (PASW) version 17.0, and the results presented in graphs were analyzed in the *GraphPad* Prism Program version 5.0.

3. Results

In general, the baseline characteristics were homogeneous among groups, indicating that the randomization process was satisfactory (Table 1). Among the participants included in the study, we had 3 dropouts from the placebo group, and none from the resveratrol group. The main results of the present study show that anthropometric parameters such as body weight, BMI and WC were significantly different after the three-month intervention period, for both groups (placebo and resveratrol) (Fig. 1A–C). The lipid profile, analyzed via TC, HDL, LDL, VLDL, and triglycerides levels showed that the individuals treated with resveratrol displayed significantly increased HDL-c ($p = 0.02$), reduced TC ($p = 0.03$) and VLDL ($p = 0.03$) (Fig. 2A–E).

The energetic and glycemic metabolism were investigated. Although it was possible to observe decreased insulin, glycemic and HBA1C levels in the resveratrol-treated individuals, those variables did not display statistically significant differences. Leptin levels, on the other hand, were decreased in the treated group ($p = 0.01$) (Fig. 3A–D).

It was also possible to observe that even not displaying statistically significant differences for the hepatic enzymes (AST and ALT), decreased levels of urea ($p = 0.04$) and creatinine ($p = 0.02$) were observed in resveratrol-treated participants. Uric acid and fibrinogen levels were not different among groups (Fig. 4A–F). Albumin levels were reduced in patients treated with resveratrol (Fig. 4G). Table 2 presents the detailed description of the results presented in graph bars, and Fig. 5 summarizes the study design along with the main findings.

4. Discussion

The present study is the first of our knowledge associating resveratrol oral supplementation in patients submitted to lifestyle change allied with physical activity aiming to control MetS components. The main results showed that lifestyle modification associated with resveratrol treatment produced a greater improvement in body weight, body mass index, waist circumference, total cholesterol, high-density lipoprotein, very low density lipoprotein, leptin, urea and creatinine levels as compared to improvements in body weight, body mass index, waist circumference, leptin and HBA1C levels in placebo-treated individuals. Noteworthy, both groups were submitted to the same physical activity plan, as well oriented to adopt same dietary patterns, being these parameters controlled between groups (placebo and resveratrol).

Regarding the lipid profile, the RSV treated group displayed approximately 36% less triglycerides, decreased total cholesterol, VLDL, and increased HDL levels as compared to placebo, while no significant differences were observed in the placebo group. It seems that resveratrol was able to improve the lipid profile. We know that an altered lipid profile is an important risk factor for atherosclerotic cardiovascular disease, being this alteration related to the metabolic disturbance associated [50]. In this sense, we emphasize that the Metabolic Syndrome (MetS) is a group of metabolic disturbances, being defined by the presence of central obesity and two or more of the following factors: elevated triglycerides, reduced HDL-c, increased arterial pressure or glycemic abnormalities [51]. Patients with MetS have an augmented chance to develop future cardiovascular events, cardiovascular mortality and all-cause mortality [52].

Recently, it was indicated that the resveratrol anti-obesity effect might be related to intestinal microbiome alterations and its consequences [53]. It is also proposed that an altered microbiome may promote activation of brown adipose tissue and browning of the white adipose tissue [22,25].

In the present study we observed significant differences in the anthropometric factors (body weight, BMI and WC) in both groups (placebo and resveratrol). These findings are extremely relevant considering that several studies already showed that abdominal obesity is more correlated to the risk of severe diseases and higher mortality as compared to gluteofemoral obesity, regardless of total body fat [22,46,54,55].

Abdominal circumference measurement is the indirect anthropometric method used to reveals the visceral fat content. It is known that central or abdominal obesity, based on WC, is the best predictor of more adverse effects for health than general obesity, determined by BMI [6]. A randomized clinical trial, double-blind, placebo controlled, performed with 24 patients with MetS showed that resveratrol was able to decrease weight, BMI, fat mass, waist circumference, insulin area under the curve and total insulin secretion [56]. In our study we also observed a significantly decrease in visceral fat, as verified by a reduced WC.

Considering the glycemic metabolism we verified a non-statically but important decrease on insulin, glucose and HBA1C levels, after resveratrol supplementation. Liu et al. (2014) showed in a meta-analysis, which included studies comprising 388 individuals, that resveratrol significantly improved the glucose control and insulin sensitivity in diabetic participants, but did not report effects on individuals without diabetes [57].

It was also verified improved leptin levels after resveratrol treatment ($p = 0.01$). It is well known that adipose tissue excessive accumulation and the persistence of low-grade inflammation are typical characteristics observed in obesity. The adipose tissue is recognized as a metabolically active endocrine organ involved in the production of several bioactive molecules capable to modulate target-organs [58]. Leptin plays a central role on the metabolic regulation, energy expenditure and glucose homeostasis. The high leptin levels are usually accompanied by negative regulation of hypothalamic receptors and leptin signaling dysfunction so called: “leptin resistance”, during obesity [59]. In this sense, the resveratrol treatment may reduce blood leptin concentrations [60], and seems to improve leptin resistance.

Additionally, it was possible to observe an important decrease in urea and creatinine levels. It is well established that diabetic nephropathy is a common complication of the Metabolic Syndrome. Kim et al. showed that resveratrol prevents diabetic nephropathy in db/db mice, via AMP-activated protein kinase (AMPK) phosphorylation and Sirtuin 1/Peroxisome Proliferator-activated Receptor Gamma Coactivator-l alpha (SIRT-1/PGC-1) activation, which seems to prevent the kidney lipotoxicity-associated apoptosis and oxidative stress [61].

In the present study we observed that the weight loss obtained by the synergic action of resveratrol supplementation, dietary intervention (calorie restriction of approximately 500 cal/day) along with the adoption of physical activity for at least 150 min a week, were beneficial in the obesity treatment, especially in the MetS components.

We conclude that the dietary supplements use, especially the resveratrol, may be beneficial as an adjunct in the MetS and obesity treatment, especially when allied to healthy habits and the practice of physical activity. Furthermore, these interventions are affordable and easily implemented in extra-clinical contexts. In this sense, the

establishment of behavioral and lifestyle changes (diet, and physical activity) along with the supplementation with polyphenols, such as resveratrol, might be a choice for individuals who need affordable methods to decrease the MetS' associated risks. Our conclusions must acknowledge, however, the present study small sample size, which may represent an important limitation. Thus, additional clinical studies are necessary to corroborate, and expand related findings.

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Declaration of competing interest

The authors declare no conflicts of interest.

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