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The effects of resveratrol on metabolic status in patients with type 2 diabetes mellitus and coronary heart disease

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Abstract

This study was performed to investigate the effects of resveratrol on metabolic status in patients with type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD). This randomized, double-blind, placebo-controlled trial was performed in 56 patients with T2DM and CHD. Patients were randomly divided into two groups to receive either 500 mg resveratrol/day (n=28) or placebo (n=28) for 4 weeks. Resveratrol reduced fasting glucose (β -10.04 mg/dL; 95% CI, -18.23, -1.86; P=0.01), insulin (β -1.09 μIU/mL; 95% CI, -1.93, -0.24; P=0.01) and insulin resistance (β -0.48; 95% CI, -0.76, -0.21; P=0.001), and significantly increased insulin sensitivity (β 0.006; 95% CI, 0.001, 0.01; P=0.02) when compared with the placebo. Resveratrol also significantly increased HDL-cholesterol levels (β 3.38 mg/dL; 95% CI, 1.72, 5.05; P<0.001) and significantly decreased total-/HDL-cholesterol ratio (β -0.36; 95% CI, -0.59, -0.13; P=0.002) when compared with the placebo. Additionally, resveratrol caused a significant increase in total antioxidant capacity (TAC) (β 58.88 mmol/L; 95% CI, 17.33, 100.44; P=0.006) and a significant reduction in malondialdehyde (MDA) levels (β -0.21 μmol/L; 95% CI, -0.41, -0.005; P=0.04) when compared with the placebo. Resveratrol upregulated PPAR-γ (P=0.01) and sirtuin 1 (SIRT1) (P=0.01) in peripheral blood mononuclear cell (PBMC) of T2DM patients with CHD. Resveratrol supplementation did not have any effect on inflammatory markers. 4-week supplementation with resveratrol in patients with T2DM and CHD had beneficial effects on glycemic control, HDL-cholesterol, total-/HDL-cholesterol ratio, TAC and MDA levels. Resveratrol also upregulated PPAR-γ and SIRT1 in PBMC of T2DM patients with CHD.

Keywords: Resveratrol, coronary heart disease, type 2 diabetes mellitus, HDL-cholesterol, antioxidant capacity

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Introduction

Type 2 diabetes mellitus (T2DM) is one of the most wide spread chronic diseases in almost all countries and is one of the biggest global public health problems [1, 2]. T2DM increases the risk of micro- and macrovascular disease [3, 4]. Coronary heart disease (CHD) is one of the major complications related to T2DM [5, 6]. T2DM is associated with several metabolic complications, including not only hyperglycemia, but also insulin resistance, dyslipidemia, increased inflammatory cytokines and oxidative damage [7]. Both T2DM and CHD are multifactorial caused diseases which, beside the environmental factors, are caused by interference of many genes having impact on pathogenesis through different mechanisms and pathways [8, 9].

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a naturally occurring polyphenolic compound originating from food sources, particularly from different plants such as berries, grapes, rhubarb and peanuts. After it gained popularity in 1992 different possible targets for its pharmacological effects have been identified [10, 11]. Some observational studies have shown that resveratrol has several effects in the prevention and treatment of a wide variety of metabolic diseases. These benefits are wide ranging and according to some indications include anticancer, antioxidant, anti-inflammatory, anti-diabetic, cardioprotective and even maybe anti-aging effects [12]. Previous evidence has shown that resveratrol supplementation can decrease the risk of CHD and improve serum lipids [13, 14]. Moreover, resveratrol is thought to activate sirtuin 1 (SIRT1) gene [15], inhibiting RelA acetylation and to promote inhibitor protein-κBα degradation, which decreases nuclear factor kappa B (NF-κB)-induced expression of tumor necrosis-alpha (TNF-α), interleukin (IL)-1β, IL(-6), and metalloproteases [16]. A study published several years ago reported that resveratrol is able to decrease oxidized LDL-cholesterol and apolipoprotein B. In addition, this study has demonstrated the ability to protect endothelial cells from lipid damage [17]. Resveratrol

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also increases endothelial nitric oxide (NO) production by upregulation of endothelial nitric oxide synthase (eNOS) expression, enhancement of eNOS enzymatic activity, and prevention of eNOS uncoupling [18]. It reduces endothelial oxidative stress, and endothelin-1 synthesis but it reduces oxidative stress in smooth muscle cells as well, it inhibits smooth muscle cell proliferation, it prevents arterial stiffness and vascular remodeling which can all contribute to its antiatherogenic effects and prevention of CHD [19]. However, some studies did not find any significant change on inflammatory markers, glycemic control and serum lipids in patients with T2DM after resveratrol supplementation [20].

Resveratrol possibly improves heart function by influencing inflammatory markers and oxidation process, platelet aggregation and endothelial function. This polyphenolic flavonoid has also effects on metabolic modulation [21]. Since resveratrol increases SIRT1 expression it improves glucose homeostasis and decreases insulin resistance [22, 23] but it also improves cardiac function through SIRT1 activation [24]. SIRT1 protects the heart against oxidative stress by regulating many substrates, such as tumor necrosis factor (TNF-α), nuclear factor-κB (NF-κB) and p53 [25-27]. Thus, we assumed that in diabetic patients with CHD, resveratrol may have beneficial effects on metabolic profile. Few studies investigated the effects of resveratrol supplementation in T2DM patients, but data on patients with diabetes who have CHD are scarce. The purpose of this study was to investigate the effects of resveratrol supplementation during 4 weeks on glycemic control, serum lipids, biomarkers of inflammation and oxidative stress patients with diabetes and CHD.

Methods

Study population

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This study was a randomized, double-blind, placebo-controlled trial, registered in the Iranian registry of clinical trials (http://www.irct.ir: IRCT20181029041490N1). It was performed at a cardiology clinic affiliated to Kashan University of Medical Sciences (KAUMS), Kashan, Iran, between September 2018 and March 2019. All experiments were performed in accordance with the Guidelines Helsinki. Experiments were approved by the ethics committee at KAUMS, and Iran. Informed consents were obtained from human participants of this study. Inclusion criteria were as follows: patients with T2DM, aged 40-85 years old with proven 2- and 3-vessel CHD. Diagnosis of T2DM was made according to the criteria of American Diabetes Association [28]. Exclusion criteria were: consuming resveratrol three months prior to the intervention, taking antioxidant and/or anti-inflammatory supplements such as vitamin E and vitamin C, having an acute myocardial infarction or cardiac surgery in the past three months, or having renal or hepatic failure.

Study design

Participants were randomly allocated (balanced block randomization) into two groups to take either 500 mg/day resveratrol (Nutrissence, Las Vegas, USA) or placebo (Barij Essence, Kashan, Iran) (n=28 in each group) for 4 weeks. Due to the lack of evidence about the appropriate dosage of resveratrol for patients with diabetes and CHD, we used duration and the above-mentioned dose of resveratrol based on previous studies in chronic kidney disease patients [29], healthy young adults [30] and patients with ulcerative colitis [31]. Color, shape, size, and package of placebo and resveratrol were identical. Randomization assignment was conducted using computer-generated random numbers. Randomization and allocation were blinded for the investigators and patients until the final analyses were completed. The randomization and enrolling participants were performed by trained staff at the cardiology clinic. Compliance with

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the consumption of placebo and resveratrol was performed by counting the remaining capsules in the capsule containers. All patients completed 3-day dietary intake records at week 1 and 4 of intervention. For obtaining patients' nutrient intakes according to 3-day food records, Nutritionist IV software (First Databank, San Bruno, CA), which was adapted for Iranian food pattern was applied. Anthropometric measures (Seca balances, Hamburg, Germany) were recorded at the beginning of the study and after the 4-week intervention in the cardiology clinic by a trained nutritionist.

Outcomes

Insulin resistance was considered as the primary outcome, but fasting plasma glucose (FPG), insulin, the quantitative insulin sensitivity check index (QUICKI), serum lipids, gene expression of interleukin-1 (IL-1), peroxisome proliferator-activated receptor gamma (PPAR-γ), tumor necrosis factor alpha (TNF-α), transforming growth factor beta (TGF-β) and CIRT1, and biomarkers of inflammation and oxidative stress were considered as secondary outcomes. Fasting blood (15 mL) samples were taken at baseline and after the 4-week intervention at Kashan Reference Laboratory. Insulin levels were determined by ELISA kit (DiaMetra, Milano, Italy) with inter-assay and intra-assay coefficient variances (CVs) below 5%. The homeostasis model of assessment-insulin resistance (HOMA-IR) and QUICKI were calculated in accordance with the standard formula [32]. Enzymatic kits (Pars Azmun, Tehran, Iran) were used to evaluate FPG and serum lipids with inter- and intra-assay CVs below 5%. CRP levels were assessed by an ELISA kit (LDN, Nordhorn, Germany) with inter- and intra-assay CVs below 7%. Plasma total antioxidant capacity (TAC) was determined using the method reported by Benzie and Strain [33], total glutathione (GSH) by using the method described by Beutler et al. [34], and MDA

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concentrations were determined by the spectrophotometric test [35] with inter- and intra-assay CVs below 5%.

Isolation of lymphocytes, RNA extraction and cDNA synthesis

Lymphocytes were isolated using 50% percoll solution (Sigma-Aldrich, Dorset, UK) gradient by centrifugation for 20 min and 3000 rpm at 4°C [36]. Total RNA was extracted based on acid guanidinium-phenol-chloroform procedure using RNX™-plus reagent (Cinnacolon, Tehran, Iran) according to the manufacturer's instructions. RNAs was treated with DNAase I (Fermentas, Lithuania) for the elimination of any genomic DNA contamination. Three micrograms of RNA were used for cDNA synthesis with random hexamer and oligo (dT) 18 primers through RevertAid™ Reverse Transcriptase (Fermantase, Canada) in total 20 µl reaction mixture [36].

Real-time PCR analysis

Appropriate primers for IL-1, PPAR-γ, TNF-α, TGF-β, SIRT1 and glyceraldehyde-3 phosphate dehydrogenase were designed **(Table 1).** Quantitative Real-time PCR was performed by the LightCycler® 96 sequence detection systems (Roche Diagnostics, Rotkreuz, Switzerland) using 4 µl of 5× EVA GREEN I master mix (Salise Biodyne, Japan), 10 ng cDNA, 200 nM of each forward and reverse primers in final volume of 20 µl.

Statistical methods and sample size

Sample size formula for randomized clinical trial were used, where type one (α) and type two errors (β) were 0.05, and 0.20 (power=80%), respectively. In a recent study [37], 0.97 as the SD and 0.78 as the change in mean (d) of HOMA-IR were used. According to the power calculation,

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in each group 25 patients were needed; after allowing for 5 dropouts in each group, the final sample size was 30 patients in each group.

The Kolmogorov-Smirnov test was used for checking the normality of data. To determine the differences in anthropometric measures and dietary intakes between two groups, the independent-samples *t*-test was used. Multiple linear regression models were used to evaluate treatment impacts on study outcomes after adjusting for confounding parameters. The effect sizes were presented as the mean differences with 95% confidence intervals. Pearson Chi-square test was applied for comparison of categorical variables. P values <0.05 were considered significant. The Statistical Package for Social Science version 18 (SPSS Inc., Chicago, Illinois, USA) were used for statistical analyses.

Results

Fifty-six patients [resveratrol (n=28) and placebo (n=28)] completed the trial (**Fig.1**). The compliance rate was high; both groups took more than 90% of capsules during the trial. No adverse effects were reported in T2DM patients with CHD while consuming resveratrol.

No significant differences were seen between the groups regarding mean age, height, and weight and BMI at baseline and end-of-trial **(Table 2).** Mean smoking rate, treatment with antidiabetic (65-70% monotherapy and 30-35% combination therapy) and lipid-lowering drugs (100% statins), hypertension rate (70-78%), treatment with angiotensin converting enzymes inhibitors (ACEI) (100%), aldosterone receptor blockers (ARB) (100%), β-blockers (90-95%) and calcium channel blockers (5-10%) were not different between the two groups (Data not shown).

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Macronutrient and micronutrient intake as calculated based on 3-days food record was not significantly different between the resveratrol and control group **(Supplemental file 1).**

After the 4-week intervention, resveratrol significantly reduced FPG (β -10.04 mg/dL; 95% CI, -18.23, -1.86; P=0.01), insulin (β -1.09 μIU/mL; 95% CI, -1.93, -0.24; P=0.01) and HOMA-IR (β -0.48; 95% CI, -0.76, -0.21; P=0.001), and significantly increased QUICKI (β 0.006; 95% CI, 0.001, 0.01; P=0.02) when compared with the placebo **(Table 3).** In addition, resveratrol administration significantly increased serum HDL-cholesterol levels (β 3.38 mg/dL; 95% CI, 1.72, 5.05; P<0.001) and significantly decreased total-/HDL-cholesterol ratio (β -0.36; 95% CI, -0.59, -0.13; P=0.002) when compared with placebo. Resveratrol also caused a significant elevation in TAC (β 58.88 mmol/L; 95% CI, 17.33, 100.44; P=0.006) and a significant reduction in plasma MDA levels (β -0.21 μmol/L; 95% CI, -0.41, -0.005; P=0.04) when compared with the placebo. Resveratrol supplementation did not affect other metabolic parameters.

Resveratrol upregulated PPAR-γ (P=0.01) and SIRT1 (P=0.01) in peripheral blood mononuclear cell (PBMC) of T2DM patients with CHD, but it did not affect gene expression for IL-1, TNF-α and TGF-β **(Fig.2 &3).**

Discussion

In this study, which to the best of our knowledge is the first of its kind, 4-week supplementation with resveratrol in diabetic patients with CHD had beneficial effects on glycemic control, HDL-cholesterol, total-/HDL-cholesterol ratio, TAC and MDA. In addition, resveratrol upregulated PPAR-γ and SIRT1 in PBMC of T2DM patients with CHD.

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Effects on glycemic control and serum lipids

Our study showed that resveratrol significantly decreased FPG, insulin levels, HOMA-IR score and total-/HDL-cholesterol ratio, and increased QUICKI and HDL-cholesterol levels without affecting other lipids and lipoproteins in patients with T2DM and CHD. In addition, resveratrol upregulated PPAR-γ and SIRT1 in PBMC of T2DM patients with CHD. T2DM and CHD are frequently associated with dyslipidemia and insulin resistance [38, 39]. Similar to our findings, in another recent study resveratrol at a dosage of 480 mg/day after 4 weeks in T2DM patients significantly decreased HOMA-IR, insulin levels, but did not influence triglycerides, total- and LDL-cholesterol levels [37]. Resveratrol supplementation in overweight pregnant women after 60 days improved glucose homeostasis parameters, but also total cholesterol, LDL-cholesterol and triglycerides [40]. Moreover, a 12-week resveratrol administration (500 mg) three times per day in patients with metabolic syndrome decreased insulin concentrations [41]. In contrast to our findings, in another study a 12-week resveratrol supplementation (100 mg/day) did not affect FPG and HDL-cholesterol in T2DM patients [42]. Also, 6-month resveratrol supplementation at dosage 40 mg/day or 500 mg/day did not improve fasting glucose, glycated hemoglobin, insulin, C-peptide, free fatty acids, adiponectin nor interleukin-6 in T2DM patients when compared with placebo [43]. Resveratrol (200 mg/day) did not influence postprandial gene expression of PPAR-γ and NF-κB, neither did it modify postprandial variations in circulating inflammatory markers (C-reactive protein, IL-6, IL-8, monocyte chemoattractant protein-1) and adhesion molecules (soluble E-selectin, soluble vascular cell adhesion molecule-1, soluble intercellular adhesion molecule-1) when compared to placebo [44]. The beneficial effect of resveratrol on serum lipids may be mediated by its phenolic hydroxyls which cause oxidation of unsaturated fatty acids and decrease of circulating total and LDL-cholesterol, triglycerides and apo AI as shown in hyperlipidemic mice [45]. As mentioned earlier, anti-atherosclerotic activity of resveratrol

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probably involves also enhanced activity of PPAR-α [46], suppression of platelet aggregation [47], very moderate decrease of systolic blood pressure [48], and improvement of endothelial activity [49] which is all important particularly in T2DM patients with CVD who have very high risk for a CVD event. The novelty of our approach was that our patients were exactly those with very high risk having both T2DM and proven CVD. These patients were not analyzed previously concerning the outcomes which we have analyzed.

Effects on biomarkers of inflammation and oxidative stress

This study showed that taking resveratrol supplements during 4 weeks causes a significant increase in plasma TAC and a significant reduction in MDA levels in T2DM patients with CHD, but did not influence other biomarkers of inflammation and oxidative damage. The novelty of our study is that it was performed on patients with both T2DM and CVD which has not been done before. In accordance with our findings, several experimental studies on animals have shown that resveratrol causes a significant decrease in MDA levels [50, 51]. 6 weeks of resveratrol at dosage 500 mg/day in patients with ulcerative colitis significantly increased TAC and reduced MDA levels [52]. The results of a trial with 12-weeks resveratrol supplementation (600 mg/day) suggested that, unlike the results of our study, resveratrol did not modify antioxidative status in patients with nonalcoholic fatty liver disease [53]. Some researchers failed to detect any significant effects of resveratrol on biomarkers of inflammation and oxidative damage in obese men and non-obese women with normal glucose tolerance [54, 55]. In diabetic patients, oxidative damage and elevated inflammatory mediators are associated with endothelial dysfunction and the progression of macrovascular disease [56]. As already stated, resveratrol can protect endothelial cells from lipid damage, promote vasodilation via modulation of NO synthesis, and can inhibit platelet aggregation [57]. Resveratrol can also inhibit kappa B inhibitor kinase, which

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subsequently prevents the translocation of NF-κB into the nucleus and the activation of the respective genes encoding cytokines, chemoattractant and adhesion molecules, and proliferating signaling molecules [58] as well as reduce oxidative damage through activation of sirtuin-activating proteins, in particular SIRT-1 [59].

It has been reported that deletion of SIRT1 in hepatocytes results in increased local inflammation [60]. In an *in vivo* study, overexpression of SIRT1 significantly reduced hepatic expression of TNF-α and IL-6 after chronic high-fat feeding [61]. The antioxidant and/or anti-inflammatory effects of resveratrol play an important role in control of NF-κB activation or chromatin remodeling by modulation of histone deacetylase (sirtuins) activity and subsequently inflammatory gene expression in lung epithelial cells [62]. SIRT1 and its activators might regulate the efficiency of the NF-κB signaling [63]. Several potential mechanisms by which resveratrol might inhibit TNF-α–mediated inflammation or insulin resistance in adipocytes include: 1) suppressing TNF-α–TNF receptor (TNFR) signaling, 2) interfering with TNF-α receptor (TNFR) binding, or 3) altering the activity of proteins involved in inflammation or lipid and insulin metabolism [64]. Some studies have documented that polyphenols increase PPAR-γ expression or activity [65, 66]. Therefore, resveratrol may reduce inflammation or insulin resistance by directly interfering with TNF-α signaling or indirectly by activating PPAR-γ [64]. Another potential mechanism by which resveratrol might inhibit inflammation and insulin resistance could be via inhibition of TNF-α–mediated reactive oxygen species (ROS) production [67]. ROS increase inflammatory gene expression by activating redox-sensitive proteins, including redox-sensitive transcription factors such as NF-κB, activator protein 1 and NF-E2-related factor-2 [68] and apoptosis signal-regulating kinase-1/thioredoxin [69]. Increased ROS production by NAPDH oxidase and reduced antioxidative enzymes such as glutathione

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peroxidase (GPx) and superoxide dismutase (SOD) contribute to inflammation and insulin resistance [70]. Resveratrol seems to attenuate inflammation by inducing gene expression of antioxidative enzymes such as SOD, heme oxygenase-1 and GPx [68]. Sakurai et al.[71] indicated that oligomerized grape seed polyphenols significantly decreased inflammation by suppressing ROS production and NF-κB activation. All these effects of resveratrol might explain its beneficial activity on glycemic control, HDL-cholesterol, TAC and MDA levels in T2DM patients, particularly those with CVD.

This study has some limitations. We did not measure resveratrol levels before and after the intervention. The next limitation was that gene expression related to lipid and oxidative damage in patients with T2DM and CHD were not evaluated. Resveratrol and placebo were provided two various companies. This should be considered in the interpretation of our findings.

Conclusions

The 4-week supplementation with resveratrol in patients with T2DM and CHD had beneficial impacts on glycemic control, HDL-cholesterol, total-/HDL-cholesterol ratio, TAC and MDA levels. Resveratrol also upregulated PPAR-γ and SIRT1 in PBMC of T2DM patients with CHD.

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Abbreviations

FPG, fasting plasma glucose; GSH, total glutathione; HOMA-IR, homeostasis model of assessment-insulin resistance; HDL-cholesterol, high density lipoprotein-cholesterol; CRP, C-reactive protein; LDL-cholesterol, low density lipoprotein-cholesterol; MDA, malondialdehyde; QUICKI, quantitative insulin sensitivity check index; VLDL-cholesterol, very low density lipoprotein-cholesterol; TAC, total antioxidant capacity; GAPDH, glyceraldehyde-3-Phosphate dehydrogenase; IL-1, interleukin-1; PPAR-γ, peroxisome proliferator-activated receptor gamma; TNF-α, tumor necrosis factor alpha; TGF-β, transforming growth factor beta; T2DM, type 2 diabetes mellitus; CHD, coronary heart disease; NF-κB, nuclear factor kappa B; PBMC, peripheral blood mononuclear cell; eNOS, endothelial nitric oxide synthase; SIRT1, sirtuin 1.

Declarations:

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

Consent for publication

Not applicable.

Availability of data and material

The primary data for this study is available from the authors on direct request.

Competing interests

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The authors declare no conflict of interest.

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Author contributions

ZA and AH: Conception, design, and statistical analysis, drafting of the manuscript and supervised the study.

GN, AF, ZR, EA and FB: data collection and manuscript drafting.

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Table 1. Specific primers used for real-time quantitative PCR

Gene	Primer	Product size (bp)	Annealing temperature (C)
GAPDH	F: AAGCTCATTTCCTGGTATGACAACG	126	61.3
	R: TCTTCCTCTTGTGCTCTTGCTGG		
PPAR-γ	F: ATGACAGACCTCAGACAGATTG	210	54
	R: AATGTTGGCAGTGGCTCAG		
IL-1	F: GCTTCTCTCTGGTCCTTGG	174	56
	R: AGGGCAGGGTAGAGAAGAG		
TNF-α	F: GTCAACCTCCTCTCTGCCAT	188	52
	R: CCAAAGTAGACCTGCCCAGA		
TGF-β	F: TTGAGACTTTTCCGTTGCCG	227	56
	R: CGAGGTCTGGGGAAAAGTCT		
SIRT1	F: GGCAAAGGAGCAGATTAGTAGG	22	58
	R: CTCTGGAACATCAGGCTCATC		

GAPDH, glyceraldehyde-3-Phosphate dehydrogenase; IL-1, interleukin-1; PPAR-γ, peroxisome proliferator-activated receptor gamma; SIRT1, sirtuin 1; TNF-α, tumor necrosis factor alpha; TGF-β, transforming growth factor beta.

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Table 2. General characteristics of study participants at baseline study

	Placebo group (n=28)	Resveratrol group (n=28)
Age (y)	63.3±10.1	61.0±8.6
Height (cm)	168.6±5.0	170.0±5.8
Weight at study baseline (kg)	79.9±11.0	82.9±10.9
Weight at end-of-trial (kg)	79.9±11.1	82.7±10.8
Weight change (kg)	-0.01±0.9	-0.2±1.2
BMI at study baseline (kg/m^2)	28.1±3.4	28.6±3.1
BMI at end-of-trial (kg/m^2)	28.1±3.5	28.5±3.0
BMI change (kg/m^2)	0.001±0.3	-0.1±0.4

Data are means± SDs.

Table 3. The effect of resveratrol supplementation on metabolic status in type 2 diabetic patients with coronary heart disease

Variables	Placebo group (n=28)		Resveratrol group (n=28)		Difference in outcome measures between resveratrol and placebo treatment groups[1]	
	Baseline	Week 4	Baseline	Week 4	β (95% CI)	P[2]
FPG (mg/dL)	133.9±52.2	136.6±50.0	129.5±56.2	122.5±53.1	-10.04 (-18.23, -1.86)	0.01
Insulin (μIU/mL)	13.1±4.2	12.7±4.3	12.4±2.7	11.0±2.7	-1.09 (-1.93, -0.24)	0.01
HOMA-IR	4.3±2.5	4.1±2.5	4.0±2.0	3.4±1.7	-0.48 (-0.76, -0.21)	0.001
QUICKI	0.31±0.01	0.31±0.02	0.31±0.01	0.32±0.01	0.006 (0.001, 0.01)	0.02
Triglycerides (mg/dL)	147.5±60.7	149.9±52.9	155.7±62.9	148.3±57.8	-8.47 (-18.78, 1.84)	0.10
VLDL-cholesterol (mg/dL)	29.5±12.1	30.0±10.6	31.1±12.6	29.7±11.6	-1.69 (-3.75, 0.36)	0.10
Total cholesterol (mg/dL)	137.7±26.7	137.6±23.2	145.9±29.4	140.1±28.6	-3.77 (-11.74, 4.18)	0.34
LDL-cholesterol (mg/dL)	68.7±21.0	68.6±21.1	78.3±21.1	70.9±20.3	-4.83 (-12.20, 2.54)	0.19
HDL-cholesterol (mg/dL)	39.5±5.9	39.1±5.4	36.4±6.5	39.5±7.7	3.38 (1.72, 5.05)	<0.001
Total-/HDL-cholesterol ratio	3.5±0.8	3.6±0.7	4.1±1.1	3.7±1.0	-0.36 (-0.59, -0.13)	0.002
CRP (mg/L)	3.9±1.9	4.1±1.5	4.2±1.5	4.2±1.0	0.10 (-0.46, 0.26)	0.58
TAC (mmol/L)	924.2±118.9	919.3±146.1	906.9±103.7	960.9±123.9	58.88 (17.23, 100.44)	0.006
GSH (μmol/L)	568.4±82.3	614.3±106.6	520.9±101.5	555.4±119.9	-28.56 (-82.81, 25.68)	0.29
MDA (μmol/L)	2.9±0.5	2.8±0.4	3.1±0.9	2.8±0.8	-0.21 (-0.41, -0.005)	0.04

Data are mean ±SDs.

[1]"Outcome measures" refers to the change in values of measures of interest between baseline and week 4. β [difference in the mean outcomes measures between treatment groups (resveratrol group = 1 and placebo group = 0)].

[2] Obtained from multiple regression model (adjusted for baseline values of each biochemical variables).

CRP, C-reactive protein; FPG, fasting plasma glucose; GSH, glutathione; HOMA-IR, homeostasis model of assessment-estimated insulin resistance; MDA, malondialdehyde; QUICKI, quantitative insulin sensitivity check index; TAC, total antioxidant capacity.

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Legend to figure:

Fig.1. Summary of patient flow diagram.

Fig.2. Fold change (means± SDs) in gene expression levels of PPAR-γ, IL-1 and TNF-α in study participants who were received resveratrol supplements and placebo

P value was obtained from independent *t*-test. N=28 in each group.

Fig.3. Change (means± SDs) in gene expression levels of TGF-β and cirtuin 1 in study participants who were received resveratrol supplements and placebo

P value was obtained from independent *t*-test. N=28 in each group.

IL-1, interleukin-1; PPAR-γ, peroxisome proliferator-activated receptor gamma; TNF-α, tumor necrosis factor alpha; TGF-β, transforming growth factor beta.

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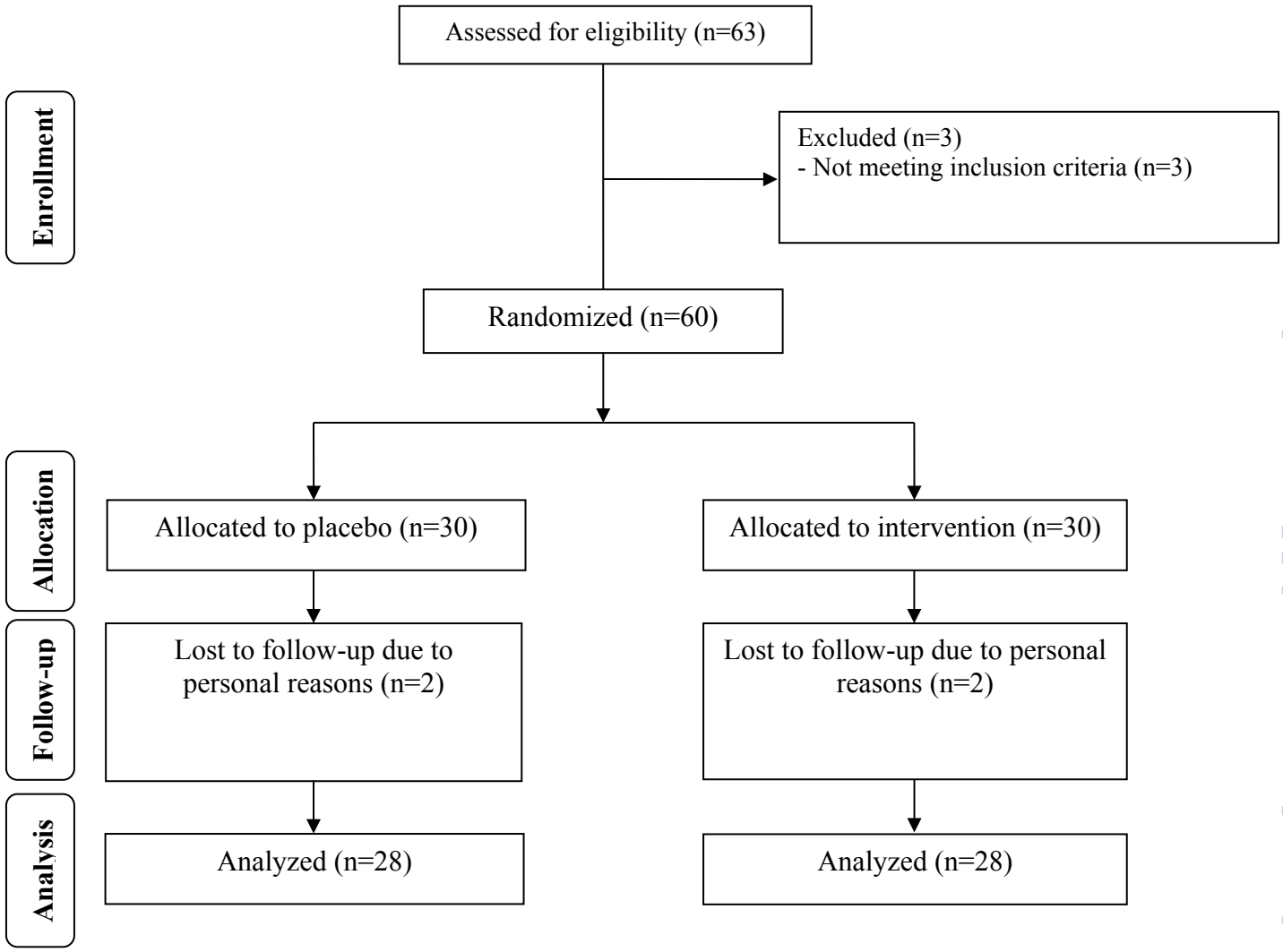

Fig.1

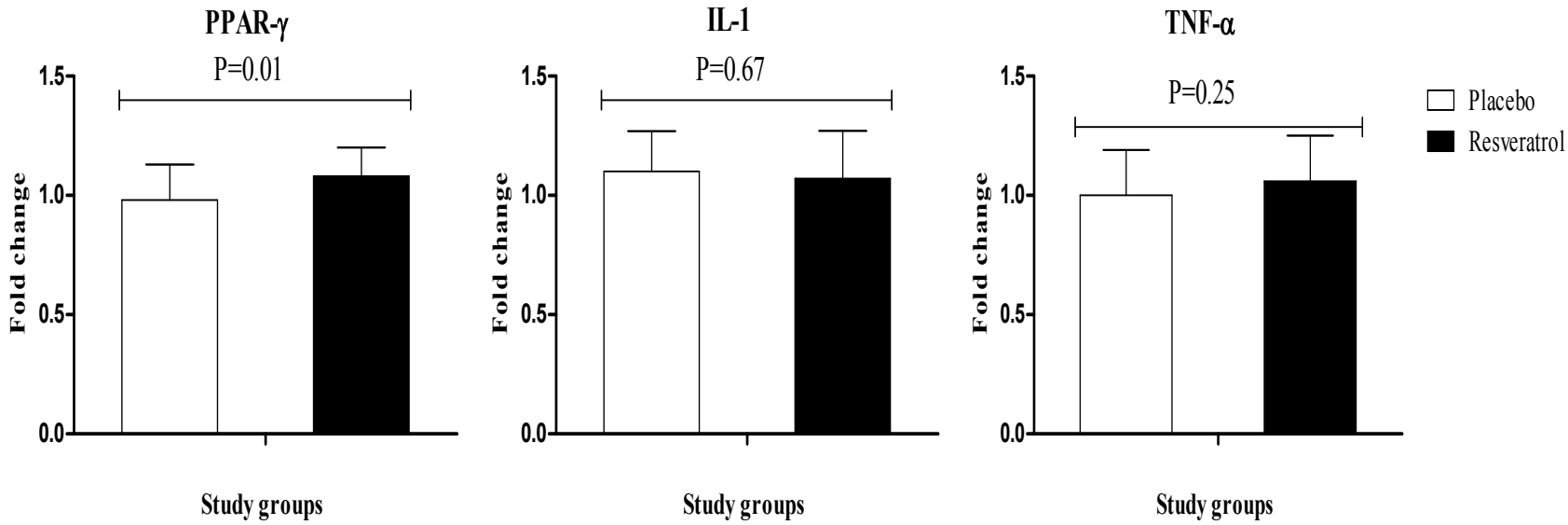

Fig.2

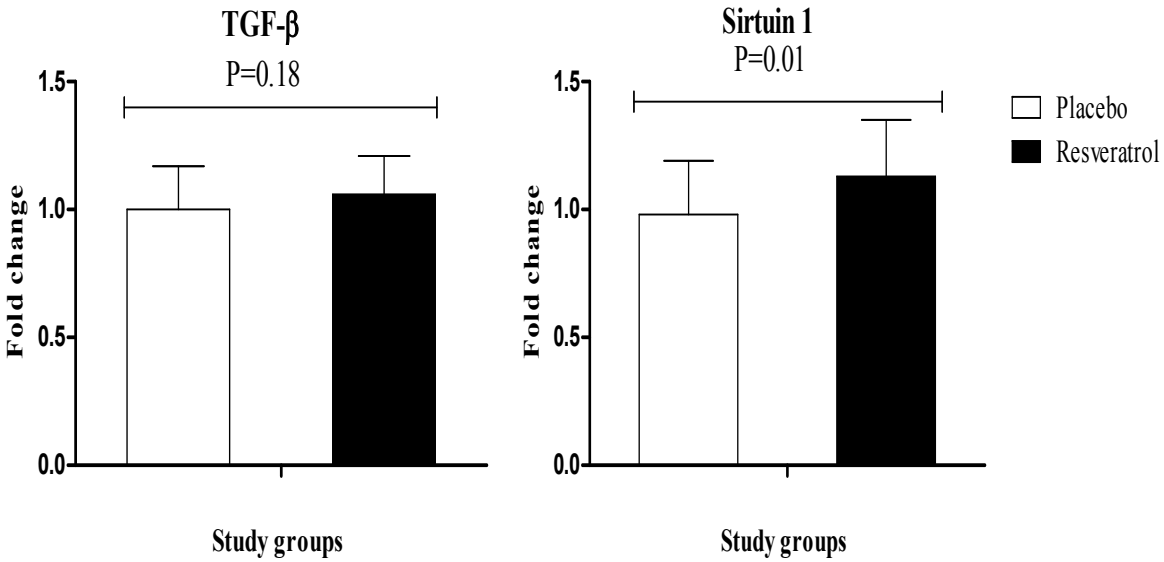

Fig.3