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ORIGINAL ARTICLE

Effects of 6 months of resveratrol versus placebo on pentraxin 3 in patients with type 2 diabetes mellitus: a double-blind randomized controlled trial

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Abstract
Aims The anti-inflammatory effects of the polyphenol resveratrol in patients with type 2 diabetes mellitus (T2DM) are controversial. Its role on pentraxin 3 (PTX3) concentrations, a human acute phase protein, has never been evaluated. Our aim was to determine whether a two-dosage resveratrol supplementation (500 and 40 mg/day) has an impact on PTX3 values in T2DM patients from a double-blind randomized placebo-controlled trial. Variations in total antioxidant status (TAS) were evaluated too.
Methods A total of 192 T2DM patients were randomized to receive resveratrol 500 mg/day (Resv 500 arm), resveratrol 40 mg/day (Resv 40 arm) or placebo for 6 months. At baseline and at the trial end, PTX3 and TAS values were determined.
Results A dose-dependent increase in PTX3 concentrations of 4.7% (Resv 40 arm) and 26.3% (Resv 500 arm), and 8.0% reduction after placebo were found. Adjusted mean differences of change versus placebo were 0.16 (95% CI 0.01–0.32) and 0.25 (0.09–0.42) in the Resv 40 and Resv 500 arms, respectively. At subgroup analyses, lower diabetes duration, aspirin, alcohol use, younger age, female gender, smoking (Resv 500 arm) and female gender and aspirin use (Resv 40 arm) were associated with higher PTX3 increments. A dose-dependent increment in TAS values in the resveratrol arms (1.4 and 6.4% for Resv 40 and Resv 500, respectively), and a reduction in placebo arm (−8.9%) were observed. Adjusted mean differences of change were 28.5 (95% CI 10.1–46.8) and 44.8 (25.4–64.1) in the Resv 40 and Resv 500 arms, respectively.
Conclusion Resveratrol supplementation increased PTX3 and TAS levels in a dose-dependent manner in T2DM patients. At present, potential clinical implications of these results remain unclear.
ClinicalTrials.gov Identifier NCT02244879.

Keywords Pentraxin 3 · Resveratrol · Type 2 diabetes mellitus · Total antioxidant status

Abbreviations

BMI	Body mass index
CV	Cardiovascular
CVs	Coefficients of variations
CRP	C-reactive protein
HbA1c	Glycated hemoglobin
IL-1	Interleukin-1
IL-6	Interleukin-6
PTX3	Pentraxin 3
SIRT	Sirtuin
TAS	Total antioxidant status

Introduction

The anti-inflammatory effects of the polyphenolic compound resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) are highly controversial [1–4]. Despite the beneficial properties against acute and chronic inflammatory states identified in animal and in vitro studies [1], human clinical trials have shown less convincing results [5–14]. The effects of

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resveratrol have been studied in the following pro- and anti-inflammatory proteins: C-reactive protein (CRP) [5–14], interleukin-1 (IL-1) [10], interleukin-6 (IL-6) [6, 7, 10–14], interleukin-10 [11, 12] and interleukin-18 [11].

To the best of our knowledge, the effects of resveratrol on pentraxin 3 (PTX3) concentrations have never been evaluated in humans. PTX3 is an evolutionarily conserved, long constituent of the molecules' pentraxins which plays a critical role in immunity and inflammation and, together with CRP, is a characteristic acute phase protein in humans [15–17]. PTX3 possesses multiple biological functions: it has been proposed as a link between innate and adaptive immunity and local and systemic responses [18]. Indeed, its role is currently highly controversial, and both a protective and a deleterious effects during pathogen invasion have been suggested [16, 17, 19]. Increased PTX3 circulating levels have been linked to endothelial dysfunction [20–22], an unfavorable prognosis in patients with systemic inflammation or infection [23], increased cardiovascular (CV) diseases incidence and mortality [24, 25]. On the other hand, PTX3 beneficial properties against acute CV diseases [18, 26, 27], neurodegenerative and brain diseases [28], and anti-angiogenic and onco-suppressive effects [29] have been reported. In dysmetabolic patients, the plasma concentrations of this protein are reported to be inversely correlated with insulin secretion, metabolic syndrome and obesity [30–34] and directly associated with weight loss [35, 36] and adiponectin levels [37]; now PTX3 is being proposed as an anti-inflammatory protein produced in response to pro-inflammatory states as an adaptive response to inflammation [31, 35]. Indeed, in diabetic patients, elevated PTX3 levels are found associated with chronic diabetes complications in some [38–41], but not all studies [42, 43]. Therefore, there is great uncertainty especially regarding the potential significance of PTX3 in patients with type 2 diabetes mellitus.

In the present paper, we report the effects of resveratrol on circulating levels of PTX3. Hence, we evaluated whether resveratrol at dosages of 40 and 500 mg/day for 6 months induces a change in the circulating concentrations of PTX3 in type 2 diabetic patients in a double-blind randomized placebo-controlled trial. The changes in total antioxidant status (TAS) were evaluated too.

Methods

From October 2013 through February 2016, participants were recruited from the Diabetic Clinic of the Department of Medical Sciences of the University of Turin, as previously reported [14]. Inclusion criteria were: type 2 diabetes mellitus, age $\geq$40 years, body mass index (BMI) <35 kg/m^2, patients on diet and/or hypoglycemic agents other than insulin. Exclusion criteria were: treatment with any antioxidant substance, treatment with insulin, anticoagulants, steroids or anti-inflammatory drugs different from aspirin, alcohol or substance abuse, uncompensated diabetes, liver or kidney diseases, presence of diabetes-related chronic complications, CV events or revascularization procedures in the previous 4 weeks, any severe chronic or life-threatening diseases, pregnancy, allergy to peanuts, grapes, wine, mulberries.

Ethics

All procedures were in agreement with the principles of the 1964 Helsinki Declaration and its later amendments. The study protocol was approved by the local ethics committee. All participants have provided their written informed consent to participate in the study.

Intervention

The study protocol had been previously described [14]. Briefly, 192 patients were randomized, respectively, to 1 capsule/day of resveratrol 500 mg/day (Resv 500 arm) for 6 months, 1 capsule/day of resveratrol 40 mg/day (Resv 40 arm) for 6 months and 1 capsule/day of placebo (totally inert microcellulose) for 6 months (placebo arm). Biotivia Bioceuticals (International SrL, Italy) prepared all the three types of capsules, which were identical in size, shape, color and taste. High-pressure liquid chromatography analyses revealed a 99.7 and a 97.9% purity of trans-resveratrol, respectively, in the 500 and 40 mg capsules and no resveratrol content in the placebo capsules.

The patients of the three arms were asked to assume everyday one capsule in the morning and to maintain for 6 months their habitual lifestyle and the diet given by the Diabetic Clinic (carbohydrates 45–60%, simple sugars <10%, fiber 20 g/1000 kcal, fats <35% total kcal, saturated fats <10% total kcal, proteins 10–20% total kcal, salt <6 g/day). All patients were allowed to keep their current hypoglycemic treatment during the trial, but they were instructed to abstain from using nutritional supplements or consuming significant amounts of resveratrol-rich foods and beverages. Compliance with the study protocol was monitored with monthly phone calls and pill counting.

All the laboratory measurements were blindly performed at the Laboratory of Metabolic Diseases of the Department of Medical Sciences, University of Turin.

Randomization and blinding

A computer-generated randomization sequence was developed by a statistician, and patients were stratified by use of acetylsalicylic acid and glycated hemoglobin (HbA1c) levels (cut point 7%); each patient was assigned a number [14].

Table 1 Comparisons on change from baseline of PTX3 and TAS values

	Placebo			Resv 40			Resv 40 versus placebo		Resv 500			Resv 500 versus placebo	
	Baseline	Trial end	Mean change from baseline	Baseline	Trial end	Mean change from baseline	Adjusted mean difference on change from baseline (95% CI)	*p*	Baseline	Trial end	Mean change from baseline	Adjusted mean difference on change from baseline (95% CI)	*p*
Number	62	58		65	59				65	62			
PTX3 (ng/mL)	0.75 ± 0.42	0.69 ± 0.43	−0.05	0.86 ± 0.63	0.90 ± 0.50	0.05	0.16 (0.01–0.32)	0.04	0.76 ± 0.39	0.96 ± 0.55	0.20*	0.25 (0.09–0.42)	0.002
TAS (μmol/L)	292.8 ± 38.4	268.1 ± 61.5	−26.2*	293.2 ± 43.6	295.5 ± 39.3	4.08	28.5 (10.1–46.8)	0.003	293.3 ± 40.2	312.3 ± 44.5	19.1*	44.8 (25.4–64.1)	<0.001

Analyses performed by using ANCOVA (adjusted for baseline level and stratification variable)

Baseline and trial end values were reported as mean ± SD, * $p < 0.05$ within-group before–after change, *t* test for dependent sample

The bottles containing resveratrol and placebo capsules were identical and were prepared by a person who did not take part in the study; a label with the number of the patient was applied to each bottle. Patients and researches who dispensed the capsules and performed the data collection and the measurements were blinded to the content of the bottles. Laboratory determinations were blindly performed.

Measurements

The measurements performed and the laboratory assays have been previously described [14].

Blood samples were collected after an overnight fast. All laboratory measurements were centralized.

The human PTX3 was measured by a ready-to-use solid-phase enzyme-linked immunosorbent assay based on the sandwich principle (Hycult Biotech, Uden, The Netherlands). The intra-assay and inter-assay coefficients of variations (CVs) were 3.6–3.8 and 4.1–4.9%, respectively. TAS measurement was performed with a colorimetric assay (ImAnOx TAS Kit, Immundiagnostik AG Bensheim, Germany). The intra-assay and inter-assay CVs were 2.0–4.0 and 2.6–3.9%, respectively.

Statistical analyses

The sample size was calculated as previously described [14]. Comparisons of change from baseline of PTX3 and TAS between the resveratrol and placebo arms were performed by ANCOVA, adjusted for the baseline measurement of the end point and the stratification variables used in the randomization (use of aspirin and HbA1c levels).

To preserve the overall type 1 error of 5%, a gatekeeping strategy was adopted accounting for the hierarchical structure of multiple comparisons in the first step. The Resv 500 arm was first compared with placebo, and only if this test was statistically significant at $p < 0.05$, a comparison between Resv 40 arm and placebo with a test $p < 0.05$ was considered as significant. Exploratory subgroup analyses were performed to identify potential interactions with the experimental treatment according to some characteristics of the patient (age, gender), of the disease (diabetes duration, HbA1c values) and by other exposures (aspirin use, smoking, alcohol consumption).

Statistical analyses were performed using Stata 11.2 software (StataCorp LP, College Station, Texas).

Results

Out of the 192 patients enrolled [66% males' median age 66 years (interquartile range 60–70)], 65 were randomized to the Resv 500 arm, 65 to the Resv 40 arm and 62 to the

placebo arm. At the trial end, data of 62, 59 and 58 patients from Resv 500, Resv 40 and placebo arms were available, owing to the dropout of 3, 6 and 4 individuals, respectively. No serious adverse event occurred, and more than 95% compliance in all arms was detected by pill counting [14]. There was homogeneity among placebo and the resveratrol arms for the baseline variables, but, by chance, a higher proportion of females in the Resv 40 group occurred, since no stratification by gender was planned [14].

At baseline, the values of PTX3 and TAS were not significantly different among the three groups (Table 1).

PTX3

The increment in PTX3 values was 4.7 and 26.3% after supplementation with resveratrol 40 and 500 mg/day, respectively (Table 1). The adjusted mean differences of change from baseline versus the placebo group were significant for both dosages. Subgroup analyses were performed to analyze potential factors which could have modified the effects of resveratrol administration (Figs. 1, 2). Lower diabetes duration, aspirin and alcohol use, younger age, female gender and being a current smoker were associated with a higher PTX3 increment in the Resv 500 arm (Fig. 1). For females and aspirin users we recorded larger effects on PTX3 values after supplementation with resveratrol 40 mg/day (Fig. 2).

TAS

A dose-dependent increment in TAS values was observed after resveratrol supplementation: the increment was 1.4 and 6.4% in the Resv 40 and Resv 500 arms, respectively. Otherwise, a reduction in placebo arm was found (−8.9%). The adjusted mean differences of change from baseline versus the placebo group were statistically significant in both the resveratrol arms.

Subgroup analyses showed that TAS levels increased in almost all subgroups, especially in those with HbA1c ≥7% (Figs. 3, 4).

Finally, we repeated the analyses relative to PTX3 and TAS, by adjusting also for the treatment with statins and with the different hypoglycemic drugs, and the estimates of the differences between resveratrol and placebo arms did not change (data not shown).

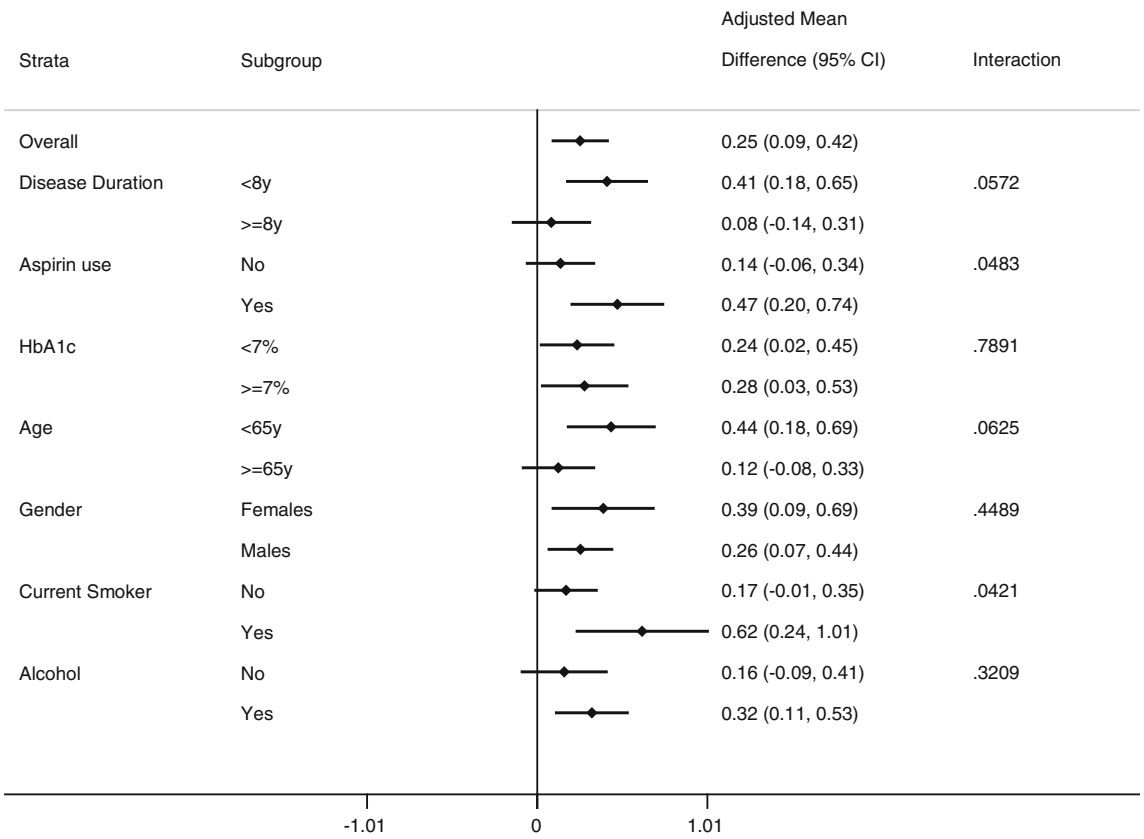

Fig. 1 Adjusted mean difference on change from baseline (95% CI) of PTX3 values (Resv 500 arm vs placebo arm)

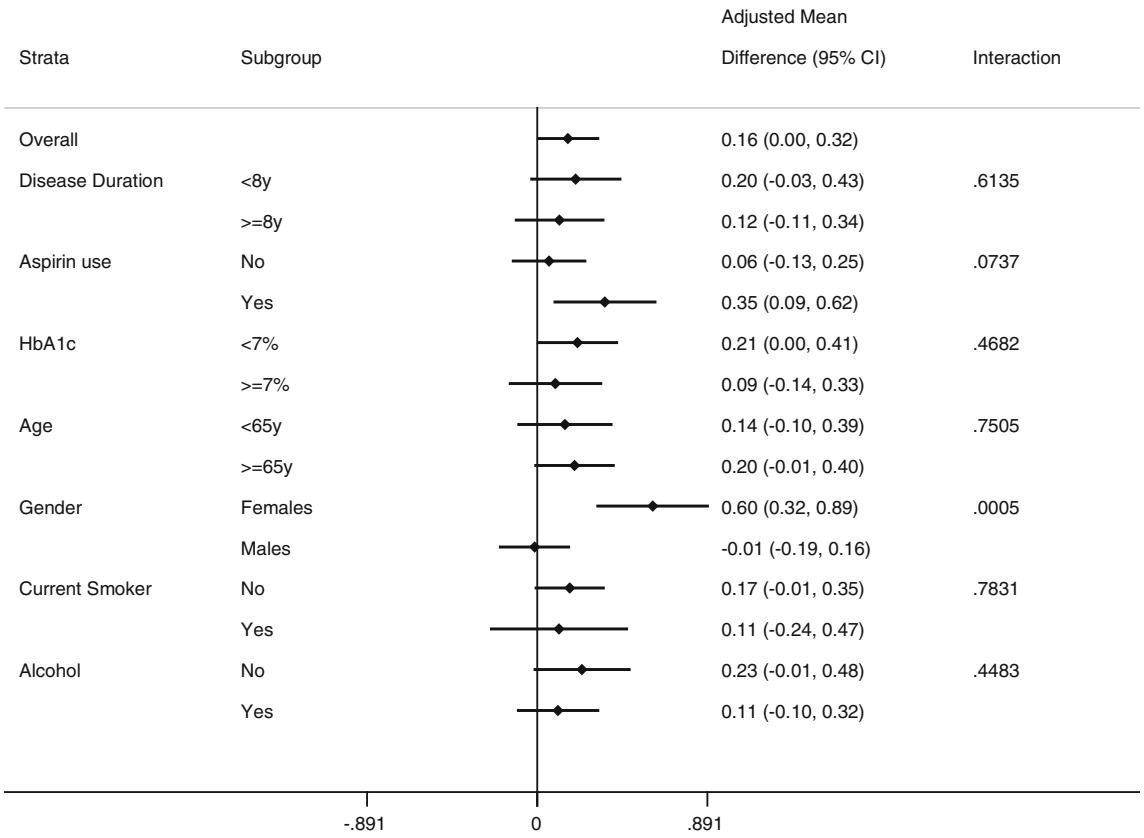

Fig. 2 Adjusted mean difference on change from baseline (95% CI) of PTX3 value (Resv 40 arm vs placebo arm)

Discussion

Resveratrol supplementation increased the concentrations of PTX3 in patients with type 2 diabetes mellitus, above all in specific subgroups of patients.

We have recently failed to detect any anti-inflammatory or metabolic benefits of resveratrol in the same patients here analyzed [14], thus putting into question, once again, the positive results previously found in animal and experimental studies [2–4].

The anti-inflammatory properties of PTX3, a molecule with multiple biological functions, are reported by an increasing number of studies [16, 19, 26–37, 44], even if some uncertainty regarding its functions remains, especially in diabetic patients [38–41]. The fact that resveratrol supplementation can lead to significant PTX3 increments at both dosages should be interpreted cautiously. One possibility is that resveratrol, rather than reducing the circulating concentrations of pro-inflammatory molecules, determined an increase in anti-inflammatory substances in humans, thus contributing to exert a beneficial role in the complex inflammatory processes.

Otherwise, the increased levels of PTX3 might represent simply an adaptive and unspecific response to the assumption of a foreign substance. This seems, however, not the case, since a proportional dose–effect of resveratrol on PTX3 values was found, and specific subgroups of patients, such as younger individuals, with lower diabetes duration and those on aspirin, as expected, showed a higher PTX3 increment after resveratrol supplementation. Type 2 diabetic patients with a long duration of disease likely show an inveterate chronic low-grade pro-inflammatory status, which may be less sensitive to this supplementation, since subclinical chronic inflammation is a common feature in the natural course of diabetes [47].

In females, characterized by increased levels of pro-inflammatory markers, and in smokers, showing a low-grade systemic inflammatory condition with elevated concentrations of inflammatory mediators and endothelial dysfunction [14], resveratrol supplementation determined a higher PTX3 increment, too.

PTX3, together with CRP, is considered as the most characteristic acute phase proteins in humans, and it is counterintuitive that resveratrol was able to change the circulating concentrations of one (PTX3), but not of the other substance (CRP) [14] in the same patients. Indeed, PTX3 is a molecule produced by several immune and vascular cells in response to pro-inflammatory signals and

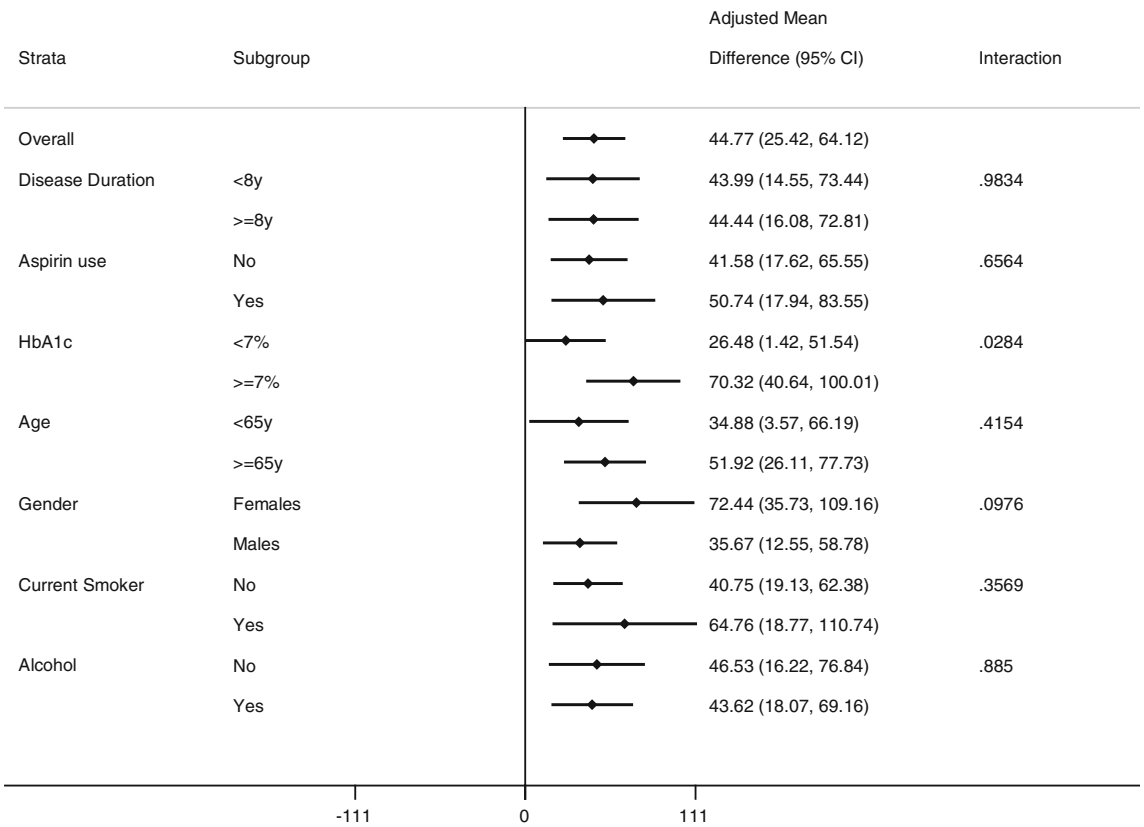

Fig. 3 Adjusted mean difference on change from baseline (95% CI) of TAS values (Resv 500 arm vs placebo arm)

by toll-like receptor engagement, but not by IL-6, differently from short constituents, such as CRP and serum amyloid P component which are synthesized in the liver mostly under IL-6 stimulation, thus suggesting for PTX3 a local rather than a systemic activation [15, 45]. Accordingly, we failed to find changes in IL-6 concentrations after resveratrol supplementation [14]. Upon inflammatory conditions, a rapid increase in PTX3 occurred by the local production of a number of different cell sources and the release of a constitutive form of PTX3 stored in specific granules of neutrophils [48]. Therefore, different and independent pathways operating on CRP and PTX3 have been reported [15, 29].

It could be hypothesized that of the multiple mechanisms proposed for the anti-inflammatory potential of resveratrol by experimental studies, such as the increased expression of sirtuin (SIRT)-1, the inhibition of the transcription factor NFκB and of NFκB-related inflammatory and autoimmune markers, the suppression of pro-inflammatory kinases, enzymes, cytokines and endothelial growth factors, the attenuation of monocyte adhesion to the endothelium, the diminished activity of T and B cells and macrophages, the decreased expression of pro-inflammatory genes, the increase in the level of anti-inflammatory eicosanoid production, the up-regulation of anti-inflammatory genes and the antioxidant and scavenger capacity [1, 5, 9, 10], resveratrol might impact more on anti-inflammatory mechanisms in humans. Indeed, the antioxidant properties of this supplement were confirmed by the significant increment in the TAS levels of all our patients after resveratrol supplementation, with a strong dose-dependent effect.

In our placebo group, we have observed a reduction in the TAS levels; those patients showed a slight increase in percent fat mass, glucose, HbA1c, CRP and IL-6 values, and a decrement in adiponectin concentrations [14]. The association between glucose circulating concentrations and oxidative stress and the generation of free radicals is well known and explains the increased lipid peroxidation and depletion of antioxidants, and the enhanced oxidative stress in diabetic patients [49, 50]. Furthermore, inflammation induces an increase in free radicals and subsequently promotes oxidative stress [51]. Therefore, it could be conceivable that the slight deterioration of the metabolic and inflammatory pattern of the patients treated with placebo might have justified their reduction in TAS values.

The role of PTX3 in humans is still under discussion; emerging evidences support protective and recovery

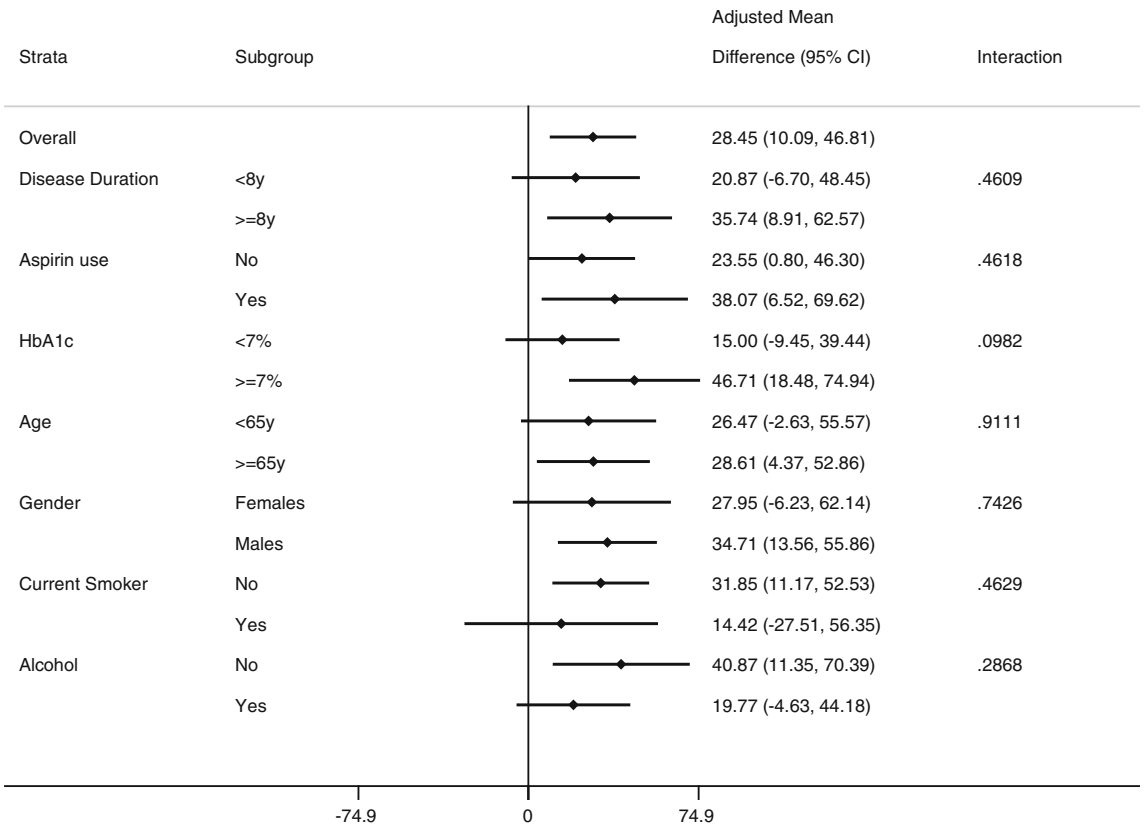

Fig. 4 Adjusted mean difference on change from baseline (95% CI) of TAS values (Resv 40 arm vs placebo arm)

actions against a wide range of pathological conditions for this molecule, which could play an adaptive anti-inflammatory response to vascular damage [16, 19, 26–37, 44].

In patients with diabetes and diabetes-related chronic complications, the reported direct association with PTX3 concentrations [38–41] might reflect the increased endovascular inflammation. Indeed, not all studies confirmed this relationship [42], and PTX3 treatment reduced renal damage in a mouse model with hyperglycemia-induced nephropathy by promoting M2 macrophage differentiation [43]. Intriguingly, treatment with liraglutide, in addition to improving the metabolic pattern of type 2 diabetic patients, increased PTX3 serum levels [46].

Resveratrol might contribute by enhancing the anti-inflammatory mechanisms in patients with type 2 diabetes, by increasing PTX3 and TAS circulating concentrations. The clinical implication of these potential effects in diabetic patients remains, however, unclear. The absolute variation we found in the circulating concentrations of PTX3 is low and quite different from the huge increment observed under experimental conditions in response to injury, infection or atherosclerotic diseases [15, 17, 23, 25, 26, 45]. Therefore, it is not known whether the changes we observed may be significant by a clinical point of view. Finally, all controversial aspects relative to the low bioavailability of resveratrol, the effect of different food matrices on resveratrol bioactivity, the high number of resveratrol metabolites with possible different significance, the great intra-individual differences in resveratrol metabolism by human gut microbiota and the uncertainty relative to the best resveratrol formulation to be used [1, 52] should be considered.

Limitations

Since plasmatic concentrations of resveratrol or its metabolites were not measured, the actual exposure to the substance cannot be determined. However, the compliance to the study protocol resulted adequate on the basis of phone calls and capsule counts. Furthermore, the proportional increment in the antioxidant capacity with increasing doses of resveratrol was consistent with the appropriate assumption of the supplement by our patients.

Most of our patients were treated with statins or metformin [14], whose effects may have affected the results. However, after controlling for the use of these drugs, the results did not change.

Conclusion

The present study demonstrated that 6-month supplementations with 500 or 40 mg/day resveratrol increased PTX3 and TAS circulating levels in type 2 diabetic patients. The potential clinical implications of these results remain at present uncertain and should be elucidated by further research.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical standard The study protocol was approved by the local ethics committee. All procedures were in agreement with the principles of the 1964 Helsinki Declaration and its later amendments.

Human and animal rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from all patients for being included in the study.

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