RESVERATROL SUPPLEMENTATION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: A PROSPECTIVE, OPEN LABEL, RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Resveratrol has been reported for its wide ranging beneficial effects on the biological system. The objective of the present study was to evaluate the effect of oral supplementation of resveratrol in patients with type 2 diabetes mellitus. A prospective, open label, randomized controlled trial was, therefore, conducted at Government Headquarters Hospital, Ootacamund, India, in which sixty two patients with T2DM were enrolled. Patients were randomized into control and intervention groups. The control group received only oral hypoglycemic agents whereas the intervention group received resveratrol (250 mg / day) along with oral hypoglycemic agents for a period of six months. HbA1C, lipid profile, oxidative stress, urea nitrogen, creatinine and protein were measured at the base line and at the end of six months. Of the 62 recruited subjects, 57 completed the study, namely 29 patients in the control group and 28 patients in the intervention group. The results reveal that supplementation of resveratrol for six months significantly decreases body weight, systolic blood pressure, total cholesterol, triglyceride, urea nitrogen and total protein. Significant increase in the level of antioxidant enzymes, namely superoxide dismutase, catalase, reduced glutathione was also observed, in addition to significant decrease in the lipid peroxidation. Resveratrol also decreases the levels of HbA1c and fasting blood glucose. However, these changes were not statistically significant. Resveratrol supplementation in patients with T2DM is found to be effective in improving associated vascular risk factors and glycemic control. Resveratrol could, therefore, be used as an effective adjuvant therapy with a conventional hypoglycemic regimen for the management of diabetes.

Keywords: Type 2 diabetes mellitus, Resveratrol, Glibenclamide, Metformin, Human

INTRODUCTION

Diabetes mellitus (DM) is one of the most common and complex diseases of worldwide significance. It has been estimated that worldwide prevalence of diabetes is 366 million people in 2011 and the number is set to increase up to 552 million people by 2030.¹ Type 2 diabetes mellitus (T2DM) is characterized by high incidence of vascular complications. Hyperglycaemia, oxidative stress, disturbances of lipid metabolism and various growth factors are among the major causes of chronic diabetic complications.² The existing T2DM treatments limit their use because of the accompanying side effects particularly weight gain, hypoglycaemia and contraindications. Moreover, none of the current antidiabetic treatments have any significant impact on the associated risk factors. There is a need, therefore, for new therapies that may improve not only hypoglycaemic effect but also the associated problems. Resveratrol (3, 5, 4'-trihydroxystilbene) is a naturally occurring phytoalexin. It has received the attention of the research community for its wide ranging beneficial effect on biological system including antidiabetic³, cardioprotective⁴, anti inflammatory and antioxidant⁵ effects. Though numerous animal studies have been reported on its wide ranging beneficial effects, only limited clinical data are available concerning its potential effects.⁶ The present study was, therefore, undertaken to investigate the effect of oral supplementation of resveratrol in patients with T2DM, in a prospective, open label, randomized controlled trial.

MATERIALS AND METHODS

Study Population

Patients with known T2DM were enrolled after explaining the objectives of the study at the screening visit after verifying the inclusion criteria. The main inclusion criteria were; patients with known T2DM, aged between 30 to 70 years, either sex, with or without co-morbidities, minimum of

6 months ongoing oral hypoglycaemic treatment (metformin and/or glibenclamide) and ≥ 3 years duration of the disease. None of the patients were on antioxidant supplementation. Patients with Type 1 diabetes, juvenile diabetes, pregnant women and lactating mothers, voluntary withdrawals and patients with any significant hepatic and renal dysfunction were excluded.

Ethics Committee Approval

The experimental protocol was approved by Institutional Human Ethical Committee, JSS College of Pharmacy, Ootacamund, Tamil Nadu, India. The trial was also registered with Clinical Trial Registry of India, Government of India (Registration Number: CTRI/2011/05/001731). Informed written consent was obtained from each subject. The study was carried out at the Outpatient Department of Government Headquarters Hospital, Ootacamund, The Nilgiris, Tamil Nadu, India, during the period of February 2011 to March 2012. Registration number of clinical trial: CTRI /2011/05/001731

Study Design

A summary of study design is shown in Figure 1. The study design was prospective, open label, randomized controlled involving T2DM patients. The enrolled patients were randomized by using computer assisted randomization procedure and assigned to control group and intervention group. Patients in the intervention group received 250 mg / OD resveratrol capsule (Biofort; Biotivia Bioceuticals International, USA) supplementation along with oral hypoglycaemic agents (OHAs) like glibenclamide and / or metformin for a period of six months, whereas patients in control group received only OHAs for a period of six months. The primary objective of the study was to assess HbA1c, body weight, body mass index (BMI), systolic and diastolic

blood pressure, lipid profile, oxidative stress, urea nitrogen, creatinine and protein. Measurements were performed at both baseline and after six months follow up.

Procedure

Demographic data and general health characteristics including height, social habit, smoking status and food habits were collected on a standard structured data collection form during the baseline visit. Height was measured to the nearest 0.5 cm and the weight to the nearest 0.1 kg. BMI was calculated as weight in kg divided by the square of height in cm.⁷ Blood pressure was measured using a mercury sphygmomanometer according to standard protocol. Subjects were seated at rest for at least 10 minutes and three measurements were taken at 5 minutes intervals. The Korotkoff V sound was used to determine diastolic blood pressure. Fasting (12 h) venous blood sample (5 mL) was collected from the patients for biochemical estimation at the baseline and after six months. HbA1c was measured by using A1C Now⁺ monitor (A1C Now⁺ Bayer Healthcare LLC, USA) and fasting blood sugar was monitored by using Dr. Morepen Gluco-One blood glucose monitor system. Triglyceride, total cholesterol and high density lipoprotein cholesterol (HDL-C) were measured by enzymatic methods of Allain and coworkers⁸. Serum low density lipoprotein cholesterol (LDL-C) was calculated by Frederickson-Friedwald's equation.⁹ Urea nitrogen was measured by the method of Murray.¹⁰ Creatinine was estimated by the method

of Bower.¹¹ Total protein was measured by the method of Kjeldahl¹² and albumin was measured by the method of Gendler.¹³ All biochemical estimations were carried with commercially available kits using semi auto analyser Merck Microlab 200. Superoxide dismutase (SOD) was measured using the method by Kakkar.¹⁴ Lipid peroxides were estimated by measuring thiobarbituric acid reactive substances (TBARs) in plasma by the method of Okhawa.¹⁵ Catalase (CAT) was measured based on the ability of CAT to inhibit oxidation of hydrogen peroxide.¹⁶ Reduced glutathione (GSH) was determined using the method by Beutler.¹⁷ Oxidative stress parameters were determined using spectrophotometric method (Shimadzu; UV-1700).

Statistical Analysis

Statistical analysis was performed by using GNU PSPP version 0.7.5-g70514b software. Data are presented as means $\pm$ SD. A p value of less than 0.05 was taken as statistically significant. Patients were randomly allocated to control and intervention group in 1:1 ratio. Per protocol analysis was used. Kolmogorov-Smirnov goodness of fit test was used. To determine the normality of distribution Descriptive analyses were used for the baseline characteristics of populations. The Mann-Whitney U test and Wilcoxon paired rank test were used for nonparametric distributions. An independent unpaired t test and paired t test were used for numerical normally distributed data. All statistical tests were two sided.

Figure 1: Subject disposition during the trial

Table 1: Baseline characteristics of participants

Variables	Control group (n = 29)	Intervention group (n=28)	p value
Age	57.75 ± 8.71	56.67 ± 8.91	0.64
Sex (Female / male)	20 / 9	16 / 12	0.43
Education ^a	I = 10, P = 6, M = 6, S = 2, HS = 3, G = 2	I = 4, P = 6, M = 4, S = 5, HS = 5, G = 4	-
Occupation ^b	H = 12, FT = 4, PT = 5, R = 6, D = 2	H = 12, FT = 5, PT = 4, R = 5, D = 2	-
Duration of disease	6.68 ± 4.70	7.57 ± 4.56	0.37
Family history of diabetes	9	12	0.43
Smoking	6	6	0.96
Alcoholic	6	6	0.96
Non-vegetarian / Vegetarians	28 / 1	24 / 4	0.46
Co morbidity	18	17	0.93

^a / Illiterate, P Primary, M Middle, S Secondary, HS Higher Secondary, G Graduate ^b H House wife, FT Full Time, PT Part Time, R Retired, D Disable to work
Results are expressed as means ± SD, median and (range) or absolute numbers, as applicable

Table 2: Biochemical and Clinical Variables at Baseline and After Six Months for the Control and Intervention Groups

Variables	Control group (n = 29)		P value	Intervention group (n = 28)		P value
	Baseline	After 6 months		Baseline	After 6 months	
Body weight (kg)	63.10 ± 9.02	63.62 ± 9.20	0.01**	64.78 ± 9.25	63.10 ± 8.49	0.002**
BMI (kg / m ²)	24.92 ± 3.05	24.97 ± 2.98	0.94	24.66 ± 3.57	24.13 ± 3.25	0.017**
Fasting blood glucose (mmol / l)	10.11 ± 2.56	11.24 ± 2.59	0.10	11.82 ± 3.58	11.22 ± 3.71	0.38
HbA1c (mmol / mol)	72 ± 3	78 ± 7	0.23	86 ± 7	85 ± 5	0.93
Systolic blood pressure (mmHg)	134.51 ± 14.61	138.82 ± 13.93	0.06*	139.71 ± 16.10	131.14 ± 9.86	0.01**
Diastolic blood pressure (mmHg)	78.62 ± 10.86	84.82 ± 7.33	0.0008***	81.42 ± 9.58	82.28 ± 10.82	0.64
Total cholesterol (mmol / l)	4.89 ± 0.89	5.29 ± 0.95	0.0001***	4.70 ± 0.90	4.08 ± 0.61	0.0001***
Triglyceride (mmol / l)	1.89 ± 0.59	1.95 ± 0.62	0.32	1.70 ± 0.63	1.22 ± 0.35	0.001**
LDL cholesterol (mmol / l)	2.80 ± 0.80	3.14 ± 0.79	0.0001***	2.58 ± 0.83	2.29 ± 0.50	0.05*
HDL cholesterol (mmol / l)	1.26 ± 0.17	1.25 ± 0.16	0.49	1.37 ± 0.27	1.23 ± 0.27	0.02**
Urea nitrogen, mmol / l	10.44 ± 1.42	10.66 ± 1.13	0.09*	11.78 ± 2.11	10.59 ± 2.00	0.005**
Creatinine, (mmol / l)	83.98 ± 9.72	88.4 ± 7.07	0.01**	90.16 ± 15.02	84.86 ± 16.79	0.15
Total Protein (g / l)	76.5 ± 3.5	77.7 ± 2.80	0.001**	75.6 ± 4.6	68.6 ± 6.00	0.0001***
Superoxide dismutase (U / ml)	4.19 ± 0.67	4.05 ± 0.54	0.17	4.41 ± 0.77	7.15 ± 1.02	0.0001***
Catalase (U / mg)	7.51 ± 0.93	7.38 ± 0.87	0.01**	8.17 ± 1.48	8.20 ± 1.50	0.01**
Reduced glutathione (mmol / l)	1.28 ± 0.06	1.28 ± 0.06	0.11	1.26 ± 0.09	1.27 ± 0.09	0.0003***
Thiobarbituric acid reactive substances (nmol / ml)	6.80 ± 0.36	6.86 ± 0.35	0.89	6.99 ± 0.35	6.81 ± 0.41	0.02**

Values are expressed as means ± SD (Student's pair t test was used); *** $p < 0.001$, ** $p < 0.05$, *not quite significant

Table 3: Change in the Biochemical and Clinical Variables during the Study Period (end of the study minus baseline) for the Control and Intervention Group

Variables	Control group (n = 29)	Intervention group (n = 28)	P value
Body weight (kg)	0.51 ± 1.08	-1.67 ± 2.70	0.0002***
BMI (kg / m ²)	0.05 ± 0.44	-0.52 ± 1.10	0.01**
Fasting blood glucose, (mmol / l)	1.13 ± 1.26	-0.60 ± 3.62	0.01**
HbA1c mmol / mol	6 ± 18	-1 ± 11	0.08*
Systolic blood pressure (mmHg)	4.31 ± 12.26	-8.57 ± 17.29	0.008**
Diastolic blood pressure (mmHg)	6.20 ± 8.90	0.85 ± 9.71	0.02**
Total cholesterol (mmol / l)	0.35 ± 0.31	-0.65 ± 0.72	0.0001***
Triglyceride (mmol / l)	0.05 ± 0.28	-0.48 ± 0.69	0.0003***
LDL cholesterol (mmol / l)	0.34 ± 0.28	-0.28 ± 0.77	0.0002***
HDL cholesterol (mmol / l)	-0.01 ± 0.11	-0.14 ± 0.31	0.03**
Urea nitrogen (mmol / l)	0.20 ± 0.64	-1.18 ± 2.05	0.001**
Creatinine (mmol / l)	3.53 ± 7.07	-5.30 ± 20.33	0.03**
Total Protein, (g / dl)	1.1 ± 1.7	-7.0 ± 6.3	0.0001***
Superoxide dismutase (U / ml)	-0.13 ± 0.53	2.73 ± 0.94	0.0001***
Catalase (U / mg)	-0.12 ± 0.26	0.07 ± 0.15	0.001**
Reduced glutathione (mmol / l)	-0.002 ± 0.007	0.005 ± 0.012	0.009***
Thiobarbituric acid reactive substances (nmol / ml)	0.003 ± 0.13	-0.18 ± 0.23	0.0005***

Values are expressed as means ± SD, Mean values were significantly different from control group (independent sample *t* test or Mann-Whitney *U* test):

*** $p < 0.001$, ** $p < 0.05$

RESULTS

Out of the 32 patients in the control group, 2 moved to other places because of job relocation and 1 discontinued for personal reasons. Of the 30 intervention subjects, 2 were lost during the follow up. In total, data for 29 patients on control group and 28 patients for intervention group were used for the analysis at the end of six months. In the control group 3 patients were on metformin, 3 on glibenclamide and 23 were on the combination of these two drugs. Among the control group 18 patients had hypertension co-morbidity. In the intervention group 5 patients were on metformin, 5 on

glibenclamide and 18 on the combination of these two drugs. In the intervention group 17 patients had hypertension co-morbidity. Table 1 shows the baseline characteristics of the enrolled patients. No significant differences were observed between the control and intervention groups at the baseline. Table 2 shows the biochemical and clinical variables at baseline and after six months of study in both the groups. The data reveal that significant changes in the body weight ($p = 0.002$), BMI ($p = 0.01$), systolic blood pressure ($p = 0.01$), total cholesterol and triglyceride ($p < 0.001$), urea nitrogen ($p = 0.01$) and total protein ($p = 0.01$) after six months of

resveratrol supplementation. Resveratrol supplementation significantly increases the level of SOD, CAT and GSH and decreases the level of TBARs. No statistical significant change was observed in fasting blood glucose, HbA1c level and creatinine level within the group after six month of supplementation.

Table 3 shows changes in the biochemical and clinical variables during the study period for the control and intervention group. The results reveal that significant differences between the control and the intervention group with respect to all the variables except HbA1c level. Resveratrol supplementation decreases the level of HbA1c. The change, however, is not quite significant.

DISCUSSION

The effect of resveratrol as a supplement in patients with T2DM was studied for the first time in this clinical trial carried out in India. Our results reveal that daily oral supplementation of resveratrol in patients with T2DM for a period of 6 months significantly reduces body weight, BMI, systolic blood pressure, total cholesterol, triglyceride, urea nitrogen and total protein. Earlier studies have reported hypoglycemic effect of resveratrol^{18,19} though some investigations have observed a contrary effect.²⁰ The present study reveals that resveratrol supplementation does decrease HbA1c level and fasting blood glucose level. The change, however, is very small and statistically not significantly. But any small change can also be very beneficial in controlling long term complications. The mechanism of hypoglycemic effect of resveratrol is still not clear though some proposal have been made.²¹⁻²⁴ Diabetes is associated with a high risk for micro vascular and macro vascular complications with a high risk of premature death. Not only hyperglycaemia but also disturbances of lipid metabolism are among the major causes of chronic diabetic complications. The present study reveals that resveratrol supplementation significantly decreases total cholesterol, triglyceride and LDL cholesterol. During the study period, it was observed that the systolic blood pressure in the control group increases significantly while in the intervention group it decreases significantly. An earlier study reports that resveratrol reduces dyslipidemia and has been described as an efficient antihypertensive agent.⁵ In the present study, a significant change was observed in the body weight of T2DM patients after six months of resveratrol supplementation. It has been reported that resveratrol prevents diet induced obesity.²⁵ It has also been suggested that longer duration of treatment with resveratrol significantly reduces the body weight.⁵ Oxidative stress also plays a central role in the development of diabetic complications. In humans, the antioxidant system includes a number of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), non enzymatic antioxidant such as reduced glutathione (GSH). Altered antioxidant enzyme levels have been reported in patients with diabetes mellitus.²⁶ In the present study, resveratrol supplementation significantly increases the levels of SOD, CAT and GSH. The activation of CAT and GSH activity may possibly be due to the ROS scavenging activity of resveratrol.²⁷ It is also possible that resveratrol allows an increase in the expression of antioxidant enzyme levels as reported earlier with antioxidants like vitamin C and E.²⁸ Cao and Li have investigated the mechanism underlying the protective effect of resveratrol in various cardiovascular disorders and demonstrated that a number of endogenous antioxidants and phase 2 enzymes including SOD, CAT and GSH can be induced by a low

concentration of resveratrol.²⁹ In another study, it has been reported that resveratrol possesses antioxidative enzyme activating potential. Resveratrol supplementation also decreases lipid peroxidation in the T2DM patients. Our results are in agreement with an earlier report.³⁰ The strength of this study is its prospective randomized control design which decreases the probability of confounding as the baseline data reveal equal distribution of covariates. Our study has some limitations in that it is an open label trial and the sample size is small. We did not include insulin related parameters, daily intake and daily energy consumption. In addition, no manipulation checks were included. Study participation may also evoke motivation for life style changes in the individual, irrespective of the treatment. Our finding, therefore, may not be generalised to populations of other ethnicities and may need to be confirmed in other independent cohorts with larger sample size and different ethnic groups. This is only a preliminary clinical study to evaluate the effect of resveratrol in patients with T2DM. In conclusion, the results of the present study suggest that resveratrol supplementation may improve the associated risk factors and glycemic control in patients with T2DM. Resveratrol can, therefore, be used as an effective adjuvant therapy with a conventional hypoglycemic regimen to treat T2DM. Our preliminary study provides data about the possible clinical effects of resveratrol supplementation on the glycemic and cardiovascular risk factors control in T2DM patients and a base for future studies with larger number of patients and longer duration.

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