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The Impact of Resveratrol Supplementation on Blood Glucose, Insulin, Insulin Resistance, Triglyceride, and Periodontal Markers in Type 2 Diabetic Patients with Chronic Periodontitis

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The aim of this study was to investigate the impact of resveratrol supplementation along with non-surgical periodontal treatment on blood glucose, insulin, insulin resistance, triglyceride (TG), and periodontal markers in patients with type 2 diabetes with periodontal disease. In this double-blind clinical trial study, 43 patients with diabetes with chronic periodontitis were participated. Subjects were randomly allocated to intervention and control groups. The intervention and control groups received either 480 mg/day of resveratrol or placebo capsules (two pills) for 4 weeks. Fasting blood glucose, insulin, insulin resistance (homeostasis model assessment of insulin resistance), TGs, and pocket depth were measured in all subjects' pre-intervention and post-intervention. The mean serum levels of fasting insulin and insulin resistance (homeostasis model assessment of insulin resistance) were significantly lower in the intervention group compared with control group (10.42 ± 0.28 and 10.92 ± 0.9; 3.66 ± 0.97 and 4.49 ± 1.56, respectively). There was a significant difference in the mean pocket depth between intervention and control groups (2.35 ± 0.6 and 3.38 ± 0.5, respectively) following intervention. No significant differences were observed in the mean levels of fasting blood glucose and TGs between two groups' post-intervention. It is recommended that resveratrol supplementation may be beneficial as adjuvant therapy along with non-surgical periodontal treatment in insulin resistance and improving periodontal status among patients with diabetes with periodontal disease.

Keywords: type 2 diabetes mellitus; periodontal disease; resveratrol; insulin resistance.

INTRODUCTION

Diabetes mellitus and periodontal disease are known as two global common and chronic diseases (Panckeviciene *et al.*, 2014). According to the World Health Organization statistics, the prevalence of diabetes mellitus was about 382 million people in the world in 2013, reaching 438 million in 2030 (Amos *et al.*, 1997; Guariguata *et al.*, 2014). On the other hand, it is indicated that more than two-thirds of the world population are suffering from periodontal disease (Dahiya *et al.*, 2013). There is a two-way relationship between these two diseases, so that diabetes mellitus may increase the risk of periodontal disease, and vice versa (Grover and Luthra, 2013). It was reported that the prevalence of severe periodontitis is approximately 39 to 59.6% higher in patients with diabetes than in patients without diabetes (Daniel *et al.*, 2012). The risk of periodontal disease is three times greater in subjects with diabetes than in subjects without diabetes (Stanko and Izakovicova Holla, 2014). Periodontal disease is a chronic inflammatory and infectious disease, affecting tissues supporting teeth, and is characterized by gingival bleeding, pocket formation, alveolar bone destruction, connective tissue degradation, and tooth loss (Offenbacher, 1996; Kara *et al.*, 2013). Periodontal disease increases insulin resistance and thereby may disturb glycemic control (Stanko and Izakovicova Holla, 2014). In a large cohort study in Taiwan (from 2003 to 2009), a significant association was observed between metabolic syndrome and diagnosis of periodontal disease (Tu *et al.*, 2013). According to the findings of some studies, periodontal inflammation is associated with a significant increases in hemoglobin A1c, fasting blood

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sugar (FBS), and inflammatory factors in patients with diabetes mellitus (Kim *et al.*, 2013; Taylor and Borgnakke, 2008).

Gram-negative anaerobic bacteria are thought to be the primary factor in the development of periodontal disease (O'Connor *et al.*, 2011). Mouthwash antibiotics are widely used to control periodontal disease: however, excessive use of antibiotics may lead to bacterial resistance against them; therefore, a new treatment strategy is needed. Natural ingredients derived from plants such as polyphenols are widely considered for the treatment of periodontal disease (Rizzo *et al.*, 2012). In addition, the importance of dietary factors in periodontal disease was identified (Zare Javid *et al.*, 2013). Intake of nutrients with antioxidant properties along with other treatments in periodontal disease can play a useful role in coping with the oxidative stress leading to injured oral tissues including teeth (Dahiya *et al.*, 2013).

Resveratrol (3, 5, 4′-trihydroxystilbene) is a polyphenol belonging to the class of stilbenes. It has phytoalexin properties as it is produced by plants in response to stress conditions including bacterial and fungal infections. *Polygonum cuspidatum* (the richest source of resveratrol) is a plant and is known as an herbal medicine (Bhatt *et al.*, 2012). Resveratrol exists in foods such as grapes, peanuts, pistachio, and cranberry (Vallanou *et al.*, 2013; Szkudelska and Szkudelski, 2010). It is known as an anti-microbial (Fordham *et al.*, 2014), antiinflammatory, anti-apoptotic (Seo and Kim, 2015), anti-cancer substance (Nassiri-Asl and Hosseinzadeh, 2016), and osteogenic factor (UysalL *et al.*, 2011). Resveratrol may have an antioxidant effect against oxidative stress in some chronic diseases such as diabetes mellitus and cardiovascular disease (Brasnio *et al.*, 2011; Park *et al.*, 2009; Bhatt *et al.*, 2012). In addition, resveratrol had beneficial effects on the liver disorders and hepatic steatosis by extenuating oxidative stress and reducing hepatic fibrosis (Khazaei *et al.*, 2016; Faghihzadeh *et al.*, 2014; Faghihzadeh *et al.*, 2015b). Furthermore, pharmacological effects were observed for resveratrol (Bedada *et al.*, 2016; Bedada and Neerati, 2016).

As it is assumed that in patients with periodontal disease, there may be a resistance to antibiotics; resveratrol with a strong anti-microbial and antiinflammatory properties can play an important role in the treatment process. Despite a higher annual sale of resveratrol supplement in the United States, there are only a few human studies about its beneficial effects (Timmers *et al.*, 2013). Based on the results of the limited human and animal studies carried out on diabetic subjects, it was reported that resveratrol can reduce insulin resistance, plasma glucose, hemoglobin A1c, FBS, and inflammatory factors, and also, it may improve insulin sensitivity (Hausenblas *et al.*, 2015). There are many studies carried out to investigate the effects of non-surgical periodontal treatment (NST) on recovery of metabolic status in these patients. Also, there are only a few studies investigating the impact of nutrition including the protecting effects of resveratrol on periodontal disease (O'Connor *et al.*, 2011; Rizzo *et al.*, 2012; Park *et al.*, 2009; Tamaki *et al.*, 2014). Therefore, the present study aimed to evaluate the effects of resveratrol supplementation in adjunct with non-surgical treatment of periodontal status on FBS, insulin, insulin resistance [homeostasis model assessment of insulin resistance (HOMA-IR)], triglycerides (TGs), and pocket depth (PD) in patients with diabetes with periodontal disease.

MATERIALS AND METHODS

Samples and study design. This randomized double-blind, placebo-controlled, clinical trial was conducted in Ahvaz Golestan hospital, Iran. The patients with diabetes referred to Endocrinology clinic with symptoms of periodontal disease were referred to dental clinic for further diagnosis. With a power of 95%, the total number of required subjects for this study was 40 people. The HOMA-IR (Brasnio *et al.*, 2011) was used for sample size calculation. With regards to the inclusion and exclusion criteria, 50 patients (36 female patients and 14 male patients) were recruited. Subjects were randomly (block design) allocated into intervention group ($n=25$) and control group ($n=25$).

Inclusion criteria included age between 30 and 60 years old, body mass index (BMI) of 18.5 to 30 kg/m^2, patients with confirmed diabetes mellitus (no more than 5 years since diagnosis), fasting blood glucose lower than 22 mmol/L, and moderate periodontal disease. Exclusion criteria included suffering from diabetes mellitus complications such as kidney failure, pregnancy, breastfeeding, traveling for more than 2 weeks, smoking, using immunosuppressive medications, using insulin, periodontal treatment history during the past 6 months, using any antioxidants (for example, vitamins C, E, A, beta-carotene, α-tocopherol, and selenium), and considerable changes in diet over the past 6 months. This clinical trial study has been submitted in Iranian Registry of Clinical Trials (IRCT ID: IRCT2015012420765N1). This study was approved by the ethics committee of the Research Deputy of Ahvaz Jundishapur University of Medical Sciences (reference no. UR1393.364ajums.rec). A signed consent form was also obtained from all subjects at the beginning of study. The intervention and control groups received either 480 mg/day of resveratrol or placebo capsules (two pills) for 4 weeks. Resveratrol capsules (480 mg Polygonum cuspidatum providing 240 mg of resveratrol) were purchased from *Herbafit*. Each capsule [ingredients: Polygonum cuspidatum extract (72%) with at least 60% trans-resveratrol, gelatin, microcrystalline cellulose (filler), and magnesium stearate]. Placebo capsules contained 480 mg of starch. All subjects were monitored and contacted three times a week by telephone to ensure that they were using prescribed capsules. During the study, all subjects used any usual blood glucose-lowering medications prescribed already. Moreover, all subjects underwent the non-surgical treatment (included removal of dental plaque, scaling, and root planning) for periodontal disease. In addition, some instructions for dental hygiene (such as how to brush and use dental floss and mouthwash correctly) were provided to all subjects. This clinical trial did not conform to the standards reported in the Consolidated Standards of Reporting Trials guidelines. Therefore, that future trials should conform to

the Consolidated Standards of Reporting Trials guidelines (Izzo *et al.*, 2016).

Anthropometric and nutritional assessments. Anthropometric indices including height, weight, and waist–hip ratio were measured at the beginning and end of the study. Weight was measured by a Seca scale (Germany), to the nearest 0.1 kg, and height was measured by using a stadiometer to the nearest of 0.1 cm. Waist circumference (widest area between the edge of lower rib and iliac corset) and hip circumference (the largest pelvic girth) were measured to the nearest 0.1 cm. A 24-h dietary recall was also obtained for dietary assessment at the beginning and end of the study.

Biochemical measurements. A fasting venous blood sample (5 mL) was obtained from all subjects prior to and following intervention. All samples were centrifuged, and serum samples were maintained in −70°C freezer until the day of analysis except some sample for analyzing FBS. Serum levels of FBS, insulin, insulin resistance (HOMA-IR), and TG were evaluated. Fasting blood sugar was immediately measured by enzymatic method by using laboratory kits (Pars Azmoon, Tehran, Iran) and an auto-analyzer. Serum levels of insulin was determined by ELISA method by using laboratory kit (Monobind, USA). Triglyceride was also measured by colorimetric method by using laboratory kits of (Pars Azmoon, Tehran, Iran). The HOMA-IR has proved to be a robust tool for the surrogate assessment of insulin resistance. The HOMA-IR was calculated by the following formula (Gayoso-Diz *et al.*, 2013):

$$HOMA\text{-}IR = Fasting\ \ glucose(\text{mmol/L}) \times fasting\ insulin\,(\mu\text{U/mL})/22.5$$

Evaluation of periodontal status. Probing depth (PD) was measured by a single, calibrated examiner at six sites per tooth: mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, and distolingual sites. The PD was recorded by using a University of North Carolina No. 15 manual periodontal probe. Full mouth clinical measurements were conducted at baseline. Ten selected sites with the probing depth of ≥4 mm were randomly selected from at least three of the quadrants for the clinical measurements after intervention (Zare Javid *et al.*, 2013).

Statistical analysis. Statistical analysis was performed by using SPSS (version 19). Data were reported as mean ± SD. In order to determine whether the data have a normal distribution, a visual examination of the data and a goodness of fit test (Kolmogorov–Smirnov) were conducted. Independent sample *t*-test was used to compare the results between two groups. The paired *t*-test was also used to compare the results within group pre-intervention and post-intervention. The confidence interval and power were considered at 95% and 95%, respectively. *P*-value lower than 0.05 was considered as significant.

RESULTS

Fifty patients were recruited in this study of which 43 subjects ($n = 22$ in control group and $n = 21$ in intervention group) completed the study. Seven patients did not use capsules regularly and were excluded. General and demographic characteristics of subjects are shown in Table 1. Mean age of the subjects in the intervention and control groups was 49 ± 7 and 50 ± 8 years, respectively. Subjects in the intervention and control groups had the mean BMI of 29 ± 4.9 and 28 ± 4.8 kg/m^2, respectively. There was no significant difference between two groups in the mean age, BMI, gender ratio, weight, waist circumference, hip circumference, FBS, fasting insulin, insulin resistance (HOMA-IR), and TG at baseline. No significant differences were also seen between two groups for dietary data including the intakes of energy, macronutrients, and micronutrients such as antioxidant vitamins C, E, A, beta-carotene, α-tocopherol, and selenium at baseline and after the intervention (Table 2).

Table 3 shows the biochemical parameters' pre-intervention and post-intervention in two groups. Although the mean FBS was higher in the intervention group compared with the control group's (7.9 ± 2.12 and 9.19 ± 2.78 mmol/L) post-intervention, it was not significant ($p = 0.097$). Furthermore, the mean FBS was reduced (but not significantly) in the intervention group after intervention (8.51 ± 3.13 and 7.9 ± 2.12; $p = 0.23$ mmol/L). Regarding with serum levels of fasting insulin, there was a significant difference ($p = 0.02$) between intervention and control group's (10.42 ± 0.28 and 10.92 ± 0.9, respectively) post-intervention. Moreover, insulin levels was significantly ($p = 0.03$) reduced in the intervention group's post-intervention compared

Table 1. Baseline characteristics of the subjects

Variable	Control group (n = 22)	Intervention group (n = 21)	*P-value*
Age (years)	50.9 ± 8.9	49.1 ± 7.4	0.48
Gender			
Female (N)	18	16	0.72[a]
Male (N)	4	5	
Body mass (kg)	70.95 ± 11	73.8 ± 10.2	0.38
Height (m)	1.58 ± 0.05	1.59 ± 0.09	0.8
BMI (kg/m^2)	28.3 ± 4.8	29.3 ± 4.9	0.48
WC (cm)	100 ± 8.9	101.4 ± 8.8	0.61
HC (cm)	107.5 ± 9.5	107.8 ± 8.1	0.92
FBG (mmol/l)	9.4 ± 3	8.5 ± 3	0.34
Insulin (μ/mL)	11.2 ± 1.3	11.3 ± 1.7	0.85
HOMA-IR	4.6 ± 1.3	4.2 ± 1.4	0.32
TG (mg/dl)	137.7 ± 66	147 ± 69	0.65
PD (mm)	4.06 ± 0.6	3.54 ± 0.5	0.29

BMI, body mass index; WC, waist circumference; HC, hip circumference; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglyceride; PD, pocket depth.

Values are expressed as means ± SD; $p < 0.05$ was considered as significant.

$P < 0.05$ was considered as significant using independent *t*-test between the two groups at baseline.

[a]$P < 0.05$ was considered as significant using chi-squared test.

Table 2. Mean ± SD of energy, macronutrients, and micronutrients intake

Variable		Baseline	After 4 weeks	*P-value*[b]
Energy (kcal/day)	Control group	1812.85 ± 329.7	1803.2 ± 265.6	0.85
	Intervention group	1819.81 ± 312.3	1838.54 ± 321.9	0.8
P-value[a]		0.94	0.69	
Carbohydrate (g/day)	Control group	238.72 ± 55.6	233.17 ± 49.9	0.5
	Intervention group	249.86 ± 60.5	251.5 ± 66	0.91
P-value		0.53	0.3	
Protein (g/day)	Control group	70.48 ± 29.37	72.7 ± 24.39	0.48
	Intervention group	61.4 ± 21.3	63.1 ± 19	0.72
P-value		0.25	0.15	
Fat (g/day)	Control group	65.82 ± 19.14	65.52 ± 20.43	0.9
	Intervention group	66.46 ± 24.2	66.84 ± 16.9	0.94
P-value		0.92	0.82	
Selenium (mg/day)	Control group	0.056 ± 0.047	0.056 ± 0.033	0.97
	Intervention group	0.076 ± 0.043	0.07 ± 0.04	0.62
P-value		0.14	0.2	
Vitamin A (mcg/day)	Control group	287.9 ± 348.3	335.36 ± 683.8	0.78
P-value	Intervention group	562.05 ± 1397.8	256.56 ± 235.6	0.25
		0.37	0.62	
Beta-carotene (mcg/day)	Control group	50.9 ± 142	19.7 ± 18	0.7
	Intervention group	55.4 ± 59.37	58.1 ± 56.9	0.38
P-value		0.89	0.7	
Vitamin C (mg/day)	Control group	101.5 ± 106.9	82.9 ± 108.2	0.19
	Intervention group	89.73 ± 81.8	87.8 ± 67.6	0.92
P-value		0.68	0.85	
Vitamin E (mg/day)	Control group	2.83	2.48	0.67
	Intervention group	2.93	2.72	0.56
P-value		0.9	0.6	
α-tocopherol (mg/day)	Control group	7.29 ± 3.21	7.09 ± 3.06	0.75
	Intervention group	6.67 ± 4.1	7.31 ± 2.82	0.38
P-value		0.58	0.8	

[a]$P < 0.05$ was considered as significant using independent *t*-test between the two groups at baseline and post-intervention.
[b]$P < 0.05$ was considered as significant using paired *t*-test.

Table 3. Biochemical variables at baseline and post intervention

	Control group (n = 22)			Intervention group (n = 21)			
Variable	Baseline	After 4 weeks	*P-value* [a]	Baseline	After 4 weeks	*P-value* [a]	*P-value* [b]
FBG (mmol/L)	9.42 ± 3.02	9.19 ± 2.78	0.64	8.51 ± 3.13	7.9 ± 2.12	0.23	0.097
Insulin (μ/mL)	11.23 ± 1.35	10.92 ± 0.9	0.21	11.32 ± 1.76	10.42 ± 0.28	0.03	0.02
HOMA-IR	4.64 ± 1.38	4.49 ± 1.56	0.49	4.22 ± 1.43	3.66 ± 0.97	0.025	0.045
TG (mg/dl)	137.7 ± 66	147 ± 69.3	0.42	147 ± 69.4	135 ± 60.89	0.27	0.65

FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglyceride.
Values are expressed as means ± SD.
[a]$P < 0.05$ was considered as significant using paired *t*-test.
[b]$P < 0.05$ was considered as significant using independent *t*-test between the two groups' post-intervention.

with the baseline (10.42 ± 0.28 and 11.32 ± 1.76). The mean HOMA-IR was significantly ($p = 0.045$) lower in the intervention group compared with control group's (3.66 ± 0.97 and 4.49 ± 1.56, respectively) post-intervention. Furthermore, within group comparison in the intervention group's post-intervention showed that the mean HOMA-IR was reduced significantly ($p = 0.025$) compared with baseline (3.66 ± 0.97 and 4.22 ± 1.43, respectively); however, this was not significant in the control group. There was no significant difference in TG between intervention and control groups' post-intervention (135 ± 60.89 and 147 ± 69.3 mg/dl, $p = 0.65$). Regarding the PD, there was a significant difference ($p < 0.01$) between intervention and control groups' (2.35 ± 0.6 and 3.38 ± 0.5, respectively) post-intervention. Moreover, PD was significantly reduced in the intervention and control groups after 4 weeks compared with the baseline (Table 4). Non-surgical periodontal therapy was performed for all subjects in both control and intervention groups. There was an improvement in periodontal status in both groups at the end of the study; however, this improvement was significantly greater in the intervention group compared with the control group.

Table 4. Periodontal Status at baseline and post intervention

PD (mm)	Baseline	After 4 weeks	Δ	*P-value* [a]	*P-value* [b]
Control group ($n = 22$)	4.06 ± 0.6	3.38 ± 0.5	−0.6 ± 0.47	<0.001	<0.001
Intervention group ($n = 21$)	3.54 ± 0.5	2.35 ± 0.6	−1.1 ± 0.58	<0.001	

Values are expressed as means ± SD.

Δ: difference between PD (mm) at baseline and After 4 weeks.

[a] $P < 0.05$ was considered as significant using paired *t*-test.

[b] $P < 0.05$ was considered as significant using independent *t*-test between the two groups' post-intervention.

DISCUSSION

In the present study, we found that receiving resveratrol supplementation for 4 weeks resulted in a significant decrease in insulin and insulin resistance (HOMA-IR), but not significant changes in serum levels of FBS. Therefore, it is suggested that there may be a physiological relationship between controlling periodontal infection and diabetes mellitus. Nutritional factors (such as antiinflammatory and antioxidant nutritional compounds) are known to be important factors affecting periodontal disease, so it is expected that improving nutritional habits and diet may be useful in the treatment of periodontal disease (Zare Javid *et al.*, 2013; Gayoso-Diz *et al.*, 2013). A study conducted by Sun *et al.* (2011) showed that treatment of periodontal disease in patients with diabetes led to controlling of blood sugar levels and a significant reduction in insulin resistance (Sun *et al.*, 2011), which concurs with the findings of the present study. There are also other studies to show an improvement in blood sugar after periodontal treatment (Moeintaghavi *et al.*, 2012; Telgi *et al.*, 2013). Since lipopolysaccharide (LPS) and inflammatory factors produced by bacteria may lead to insulin resistance, treatment of periodontal disease through elimination of these microorganisms can result in a reduction in these inflammatory markers and improve insulin sensitivity (Grover and Luthra, 2013; Simpson *et al.*, 2010). In agreement with our study, Brasnyo *et al*. showed that a 4-week consumption of resveratrol significantly reduced insulin resistance in patients with type 2 diabetes (Brasnio *et al.*, 2011). Mendez-Del Villar found that resveratrol supplementation in patients with metabolic syndrome resulted in a significant decrease in blood insulin area under the curve, but no significant changes were seen in the curve for glucose level (Mendez-Del Villar *et al.*, 2014). Furthermore, one study by Crandall *et al.* showed that a 4-week consumption of resveratrol supplements in patients with impaired glucose tolerance improves insulin sensitivity and factors related to blood sugar after a meal, without a significant decrease in FBS (Crandall *et al.*, 2012). Similarly, in our study, no significant decrease was observed in fasting blood glucose levels. On the other hand, in a study conducted by Chen *et al*., there was a significant decrease found in FBS after periodontal treatment in patients with diabetes (Chen *et al.*, 2012). Similarly, in a study by Debora *et al.*, NST did not have significant impact on glycemic control and FBS (Rodrigues *et al.*, 2003), which is consistent with our study. It is suggested that the beneficial effects of resveratrol is related to inactivation of nuclear factor-kB stimulated by bacterial LPS in inflamed tissue and activation of sirtuin (SIRT) and adenosine monophosphate kinase (Tamaki *et al.*, 2014). Periodontal disease is an inflammatory process, in which the leukocytes penetrate to the endothelium of inflamed periodontal tissues. It is believed that the main factor influencing inflammation is infection with oral pathogens. Bacterial LPS induce the adhesion of leukocytes in periodontal tissue endothelium through the sticky molecules. Resveratrol significantly inhibited the bacterial LPS. The main mechanism suggested for inhibition of LPS by resveratrol is non-activation of nuclear factor-kB (Park *et al.*, 2009). Sirtuin (SIRT) proteins are thought to improve mitochondrial function and energy limiting, and it is indicated that there is a direct relationship between SIRT and the beneficial role of resveratrol metabolism including the improvement of glucose metabolism and insulin sensitivity. Adenosine monophosphate kinase activated by SIRT has beneficial effects on the reduction of oxidative stress as the most important factor in insulin resistance, which results in improved insulin sensitivity and glycemic control (Vallanou *et al.*, 2013; Timmers *et al.*, 2013). Another possible mechanism is to relate resveratrol to sulfonylureas receptors and its effects on beta pancreas cells and insulin secretion (a mechanism that is similar to the effects of the glibenclamide) (Hambrock *et al.*, 2007). In Bhatt *et al*.'s study, receiving resveratrol supplementation in patients with diabetes mellitus for 3 months significantly reduced fasting plasma glucose and other risk factors related to glycemic control (Bhatt *et al.*, 2012). Movahed *et al*. showed that a short-term consumption of resveratrol significantly reduced fasting plasma glucose and insulin resistance in patients with type 2 diabetes (Movahed *et al.*, 2013). Moreover, in another study by Timmers *et al*., a 30-day consumption of resveratrol in healthy obese people resulted in a significant decrease in insulin, insulin resistance (HOMA-IR), and fasting blood glucose (Timmers *et al.*, 2011). These studies are inconsistent with the findings of the present study. The difference in the duration of intervention in these studies might be a reason for such controversial results regarding with changes in FBS. In addition, the study was conducted with resveratrol-enriched Polygonum cuspidatum extract and not highly pure resveratrol as done by the other studies, for example, Movahed *et al.* (2013), Timmers *et al.* (2011), and Bhatt *et al.* (2012). The lower purity of resveratrol used in this study could have attributed to a lack of impact of resveratrol on FBS in patients with type 2 diabetes. Therefore, further studies are suggested in future. Patients with type 2 diabetes are affected by impaired glucose and lipid metabolism, which eventually leads to dyslipidemia in these patients (Iacopino and Cutler, 2000). Also, in patients with diabetes mellitus and periodontal disease, there may be an increase in some inflammatory factors

such as IL6 and TNFα result in dyslipidemia and hypertriglyceridemia (Bastos *et al.*, 2012; Wu *et al.*, 2015). In one cohort study evaluating the relationship between metabolic syndrome and periodontal disease, Tu *et al*. showed that patients with periodontal disease have higher levels of blood TGs (Tu *et al.*, 2013). In a study conducted by Mointaghavi *et al*., no significant decrease was observed in serum TG in patients with diabetes after periodontal treatment (Moeintaghavi *et al.*, 2012). Furthermore, in a study by Crandall *et al*, no changes was observed on lipid profile including blood TGs (Crandall *et al.*, 2012). In the other study by Morten *et al*. in 2013 investigating the effect of receiving resveratrol supplements in healthy obese men, no significant changes was observed in lipid profile (Poulsen *et al.*, 2013). In a study conducted by Faghihzadeh *et al*., investigating the effect of receiving resveratrol supplements in patients with non-alcoholic fatty liver disease, no significant changes was observed in lipid profile after 12 weeks (Faghihzadeh *et al.*, 2015a).

The link between various nutrients and systemic disease has been established, but relatively little work has been performed in relating oral conditions with nutrition. Furthermore, few studies conducted on the effects of nutritional intervention in adjunct with NST on periodontal status. Several *in vitro* studies support the beneficial effects of resveratrol on periodontal disease. Similarly, in the present study, there was a significant improvement in PD post-intervention. To our best of knowledge, there was no human study about the effects of resveratrol supplementation in patients with periodontitis. In one study carried out by Nafumi *et al*., the effects of resveratrol were investigated on Wistar male rats with periodontal disease, and it was shown that resveratrol reduced periodontitis and bone loss, increased antioxidant defense, and improved inflammatory factors; therefore, resveratrol supplementation was recommended for improving periodontal status (Tamaki *et al*., 2014). In a laboratory study in 2009 in Korea, Joo Park *et al*. investigated the effect of resveratrol on LPS *Porphyromonas gingivalis*. They also suggested that resveratrol supplementation may help to remove periodontal pathogens (Park *et al.*, 2009).

There are some studies that showed the beneficial effects of antioxidant or antiinflammatory nutritional factors such as vitamin C, alpha-tocopherol, beta-carotene, Q10, omega 3, green tea, probiotics, and cranberry juice on periodontal status (Soory, 2012) Munozca *et al*. showed that receiving multi-vitamin nutritional supplement in periodontal patients resulted in a significant improvement in periodontal indices specifically in the PD (Munoz *et al.*, 2001). Similarly, in a study by HeshamEl-Sharkawy *et al*., *n*-3 polyunsaturated fatty acid supplementation led to a significant decrease in PD (El-Sharkawy *et al.*, 2010)

CONCLUSION

In the present study, resveratrol supplementation improved insulin resistance and periodontal status in patients with diabetes with periodontal disease after 4 weeks. It is suggested that using resveratrol as a dietary supplement with antiinflammatory and antibacterial properties, in adjunct with NSTs, may be helpful in controlling the periodontal status followed by controlling some complications in diabetes mellitus. Therefore, with regards to nutritional recommendations, using resveratrol supplementation may be beneficial in patients with diabetes with periodontal disease.

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Conflict of Interest

The authors have declared that there is no conflict of interest.

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