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Original Article

The Effect of Resveratrol Supplementation in Adjunct with Non-surgical Periodontal Treatment on Blood Glucose, Triglyceride, Periodontal Status and Some Inflammatory Markers in Type 2 Diabetic Patients with Periodontal Disease

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ABSTRACT

Background and Objectives: Diabetes mellitus and periodontal disease are two chronic and common diseases with close relationship together affecting public health and quality of life. The aim of this study was to investigate the effect of resveratrol supplementation in adjunct with non-surgical periodontal treatment (NST) on blood glucose, triglyceride, periodontal status and inflammatory markers in type 2 diabetic patients with periodontal disease.

Materials and Methods: This double-blind clinical trial study was conducted on 43 diabetic patients with periodontitis referred to the Endocrinology Clinic at Golestan Hospital in Ahvaz, Iran. All subjects were randomly assigned into two groups of intervention and control. The intervention and control groups received either 480 mg/d resveratrol or placebo capsules (2 PCs) for four weeks. All subjects underwent non-surgical periodontal therapy during the intervention period. Anthropometric parameters, 24-hour dietary recall, fasting blood sugar, insulin, insulin resistance (HOMA-IR), triglycerides, pocket depth (PD), IL6 and TNFα were evaluated in all subjects pre- and post-intervention.

Results: The mean serum levels of fasting insulin and insulin resistance (HOMA-IR) were significantly (P=0.02, P=0.045, respectively) lower in the intervention group compared with the control group (10.42 ± 0.28 and 10.92 ± 0.9; 3.66 ± 0.97 and 4.49 ± 1.56, respectively). Moreover, significant difference (P < 0.001) was obtained in the mean pocket depth (PD) between the intervention and control groups (2.35 ± 0.6 and 3.38 ± 0.5, respectively) post-intervention. In the intervention group, the mean serum level of IL6 was reduced significantly (P= 0.039) post-intervention (1.58 ± 1.06 and 2.19± 1.09). No significant differences were seen in the mean levels of fasting blood sugar, triglycerides, IL6 and TNFα between the two groups post-intervention.

Conclusions: It is suggested that resveratrol may be recommended as adjuvant therapy along with non-surgical periodontal treatment in diabetic patients with periodontal disease.

Keywords: Type 2 diabetes mellitus, Periodontal disease, Resveratrol, Insulin resistance, Inflammatory markers

Introduction

Diabetes mellitus and periodontal disease are known as two global common and chronic diseases (1). According to the World Health Organization (WHO) statistics, the prevalence of diabetes mellitus

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was about 382 million people in the world in 2013, reaching 438 million in 2030 (2, 3). On the other hand, it is indicated that more than 2/3 of the world population are suffering from periodontal disease (4). There is a two-way relationship between these two diseases so that diabetes mellitus may increase the risk of periodontal disease and vice versa (5). It was reported that the prevalence of severe periodontitis is approximately 39 to 59.6% higher in diabetic than non-diabetic patients (6). The risk of periodontal disease is three times greater in diabetic subjects than in non-diabetic subjects (7, 8). 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 (9, 10). Periodontal disease increases insulin resistance, and thereby may disturb glycemic control (11). It has been found that controlling blood sugar is six times lower in diabetic patients with periodontitis than in diabetic patients without periodontitis (12). It has also been indicated that type 2 diabetic patients with periodontal disease have higher levels of inflammatory markers such as IL-1β, TNFα and IL-6. These inflammatory factors may adversely alter blood glucose and lipid metabolism (13). In a large cohort study in Taiwan (from 2003 to 2009), a significant association was observed between metabolic syndrome and diagnosis of periodontal disease (14). According to the findings of some studies, periodontal inflammation is associated with a significant increase in Hemoglobin A1c (HbA1c), Fasting Blood Sugar (FBS) and inflammatory factors in patients with diabetes mellitus (15, 16). Gram-negative anaerobic bacteria are thought to be the primary factor in the development of periodontal disease (17). Several researchers have investigated the beneficial effects of non-surgical periodontal therapy including oral health education, use of antibiotics, scaling and root planning (18). 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 (19). In addition, the importance of dietary factors in periodontal disease has been identified (20). 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 (4). Resveratrol (3, 5, 4'-trihydroxystilbene, a composition of phytoalexin) is produced by polyphenol plants of Stilbene in response to stressful irritations such as fungal and bacterial infections. Polygonum cuspidatum (the richest source of resveratrol) is a root extract, and is known as a herbal medicine. Resveratrol exists in foods such as grapes, peanuts, pistachio and cranberry (21, 22). Resveratrol is known as an anti-microbial (23), anti-inflammatory, anti-apoptotic (24), anti-cancer substance and osteogenic factor (25). Resveratrol may have an antioxidant effect against oxidative stress in some chronic diseases such as diabetes mellitus and cardiovascular diseases (24, 26, 27). It is assumed that in patients with periodontal disease, there may be a resistance to antibiotics; resveratrol with a strong anti-microbial and anti-inflammatory properties can play an important role in the treatment process. On the other hand, resveratrol is known as a *French paradox*, and may lower the mortality rate caused by cardiovascular diseases (28). Despite a higher annual sale of resveratrol supplement in the United States, there are only few human studies about its beneficial effects (29). 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, HbA1c, FBS, and inflammatory factors; it may also improve insulin sensitivity (24, 27, and 30). There are many studies on the effects of non-surgical periodontal treatment on the recovery of metabolic status in these patients. Also there are only few studies investigating the impact of nutrition including the protecting effects of resveratrol on periodontal disease (17, 19, 26, and 31). In the case of the effectiveness, nutritional therapy can be used as a safest approach to prevent and treat periodontal disease. Therefore, the present study aimed to evaluate the effect of resveratrol supplementation in adjunct with non-surgical treatment of periodontal status on FBS, insulin, insulin resistance (HOMA-IR), triglycerides, pocket

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depth (PD) and inflammatory markers comprising IL6 and TNFα in diabetic patients 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 diabetic patients referring to the Endocrinology Clinic with some symptoms of periodontal disease were referred to Dental Clinic for further diagnosis. The Flowchart for this study is shown in Fig. 1. With a power of 95%, the total number of required subjects for this study was 40 people. The Homa-IR (24) was used for sample size calculation. Regarding with the inclusion and exclusion criteria, 50 patients (36 females and 14 males) were recruited. The subjects were randomly allocated into two groups of intervention (n = 25) and control (n = 25). Inclusion criteria included having age between 30 and 60 years, body mass index 18.5-30 kg/m^2, confirmed diabetes mellitus (no more than five years since diagnosis), FBS lower than 22mmol/L, and moderate periodontal disease**.** Exclusion criteria included suffering from diabetes mellitus complications such as kidney failure, pregnancy, breastfeeding, traveling more than two weeks, smoking, using immunosuppressive medications, using insulin, periodontal treatment history during the past six months, using any antioxidants, and considerable changes in diet over the past six months. 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 the study. The intervention and control groups received either 480 mg/d resveratrol or placebo capsules (2 pills) for four weeks. Resveratrol capsules (480 mg Polygonum Cuspidatum providing 240 mg resveratrol) were purchased from Herbafit. Placebo capsules contained 480 mg starch. All subjects were monitored and contacted three times a week by telephone to ensure that they were using the prescribed capsules. During the study, all subjects used any usual blood glucose-lowering medications prescribed already. Moreover, all subjects underwent the non-surgical treatment (including 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.

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 of 0.1 kg, and height was measured 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 of 0.1 cm. A 24-hour 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 pre- and post-intervention. All samples were centrifuged, and the serum samples were maintained in -70°C freezer until the day of analysis except some samples for analyzing FBS. Serum levels of FBS, insulin, insulin resistance (HOMAIR), triglyceride (TG), IL6 and TNFα were evaluated. FBS was immedietly measured by enzymatic method using laboratory kits (Pars Azmoon, Tehran, Iran) and an auto-unalyzer. Serum level of insulin was determined by ELISA method using laboratory kit (Monobind ,USA). TG was also measured by colorimetric method using the laboratory kits of Pars Azmoon (Tehran, Iran). IL6 and TNFα were measured by ELISA method using laboratory kits (eBioscience, Germany). Insulin resistance (HOMA-IR) was calculated by the following formula:

HOMA-IR =Fasting glucose (mmol/L) ×fasting insulin (μU/mL)/22.5

Evaluation of periodontal status: Probing depth (PD) was measured by a single, calibrated examiner at 6 sites per tooth: mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual and distolingual sites. The PD was recorded using a UNC-15 (University of North Carolina No. 15) manual periodontal probe. Full mouth clinical measurements were conducted at baseline. Ten selected sites with the probing depth ≥ 4 mm were randomly selected

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from at least 3 of the quadrants for the clinical measurements after intervention.

Statistical analysis: Statistical analysis was done 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 (Kolmorogov-Smirnoff) were conducted. Independent sample t-test was used to compare the results between the two groups. Paired t-test was also used to compare the results within groups pre- and post-intervention. The confidence interval and power were considered at 95% and 95%, respectively. P-values lower than 0.05 were considered significant.

Results

Totally, 50 patients were recruited of which 43 (n=22 in the control group and n=21 in the intervention group) completed the study. Seven patients did not use capsules regularly and were excluded. General and demographic characteristics of the subjects are shown in Table 1. Mean age of the subjects in the intervention and control groups was 49±7 and 50±8 years, and mean BMI of 29±4.9 and 28 ±4.8 kg/m^2, respectively. There was no significant difference between the two groups in mean age, BMI, gender ratio, weight, waist circumference, hip circumference, FBS, fasting insulin, insulin resistance (HOMA-IR), TG, IL6 and TNFα at baseline. No significant differences were also seen between the two groups for dietary data including the intakes of energy, macronutrients and micronutrients such as antioxidant vitamins C, E, and A, α-tocopherol and selenium at baseline and after the intervention (Table 2).

Table 1: Baseline characteristics of the subjects

Varieble	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[†]
Male (N)	4	5	
Weight (kg)	70.95 ± 11	73.8 ± 10.2	0.38
Height (m)	1.58 ± 0.05	1.59 ± 0.09	0.8
BMI (kg/m2)	28.3 ± 4.8	29.3 ± 4.9	0.48
Waist circumference (cm)	100 ± 8.9	101.4 ± 8.8	0.61
Hip circumference (cm)	107.5 ± 9.5	107.8 ± 8.1	0.92
Fasting blood glucose (mmol/l)	9.4 ± 3	8.5 ± 3	0.34
Insulin (µu/ml)	11.2 ± 1.3	11.3 ± 1.7	0.85
Homa-ir	4.6 ± 1.3	4.2 ± 1.4	0.32
Triglyceride (mg/dL)	137.7 ± 66	147 ± 69	0.65
IL-6 (pg/ml)	2.08 ± 0.8	2.19 ± 1	0.71
TNF-α (pg/ml)	10.56 ± 0.6	10.49 ± 0.47	0.6
PD(mm)	4.06 ± 0.6	3.54 ± 0.5	0.29

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.
[†] P <0.05 was considered as significant using chi-square test.

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

Variable		Baseline	After 4 weeks	*P-value***
Energy (kcal/d)	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**	0.94	0.69	
Carbohydrate (g/d)	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/d)	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/d)	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/d)	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/d)	Control group	287.9 ± 348.3	335.36 ± 683.8	0.78
	Intervention group	562.05 ± 1397.8	256.56 ± 235.6	0.25
	P-value	0.37	0.62	
Beta-Carotene (mcg/d)	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/d)	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/d)	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/d)	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	

*P <0.05 was considered as significant using Independent T-test between the two groups at baseline and post-intervention
**P <0.05 was considered as significant using Paired T-test.

Table 3 shows the biochemical parameters pre- and post-intervention in the two groups. Although the mean FBS was higher in the intervention group compared with the control group (7.9±2.12 and 9.19±2.78) post-intervention, it was not significant (P=0.097). Furthermore, the mean FBS was reduced (but not significantly) in the intervention group post-intervention (8.51±3.13 and 7.9±2.12; P=0.23). Regarding with the serum levels of fasting insulin, There was a significant difference (P = 0.02) between the intervention and control groups (10.42±0.28 and 10.92± 0.9 respectively) post-intervention. Moreover, insulin level was significantly (P=0.03) reduced in the intervention group post-intervention compared to the baseline (10.42± 0.28 and 11.32 ± 1.76, respectively). The mean HOMA-IR was significantly (P=0.045) lower in the intervention group compared with the control group (3.66±0.97 and 4.49±1.56, respectively) post-intervention. Furthermore, within group comparison in the intervention group showed that the mean HOMA-IR was reduced significantly (P=0.025) post-intervention compared with the 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 level between the intervention and control groups post-intervention (135±60.89 and 147±69.3 mg/dL, p=0.65). Moreover, no significant (P=0.3) difference was obtained in the mean level of IL6 between the two groups (1.58±1.06 and 1.85±0.59, respectively) post-intervention. However, in the intervention group, the mean level of IL6 was significantly (P=0.039) reduced post-

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intervention compared with baseline (1.58 ±1.06 and 2.19±1.09, respectively). Furthermore, the mean serum level of TNFα did not show a significant (P=0.25) difference betweenthe intervention and control groups (10.33±0.66 and 10.57±0.68, respectively) post-intervention. Regarding with pocket depth (PD), there was a significant difference (P<0.001) between the two groups (2.35±0.6 and 3.38±0.5 mm, respectively) postintervention. Moreover, PD was significantly reduced in the intervention and control groups after 4 weeks compared to the baseline (Table 4).

Table 3. Biochemical variables at baseline and post-intervention.

Variable	Control group (n=22)			Intervention group (n=21)			*P-value***
	Baseline	After 4 weeks	*P-value* *	Baseline	After 4 weeks	*P-value* *	
Fasting blood glucose (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 (µu/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
Triglyceride mg/dL)	137.7 ± 66	147 ± 69.3	0.42	147 ± 69.4	135 ± 60.89	0.27	0.65
IL-6 (pg/ml)	2.08 ± 0.82	1.85 ± 0.59	0.1	2.19 ± 1.09	1.58 ± 1.06	0.039	0.3
TNF-α (pg/ml)	10.56 ± 0.61	10.57 ± 0.68	0.93	10.49 ± 0.47	10.33 ± 0.66	0.2	0.25

Values are expressed as means ± SD.
*P <0.05 was considered as significant using Paired T-test.
**P <0.05 was considered as significant using Independent T-test between the two groups post-intervention.

Table 4. Periodontal Status at baseline and post intervention.

PD(mm)	Baseline	After 4 weeks	Δ	*P-value* *	*P-value* **
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.
*P <0.05 was considered as significant using Paired T-test.
**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 four weeks resulted in a significant decrease in insulin and insulin resistance (HOMA-IR), but there was no significant change in the serum levels of FBS. Furthermore, some inflammatory markers including IL6 were significantly reduced after using resveratrol supplementation (as a nutritional factor in adjunction with NST). It has previously been shown that serum level of some inflammatory markers including IL6 were high in patients with periodontal disease; such a reduction in these markers seen in this study may improve the infection occurred in periodontal status and affect blood glucose-dependent factors like insulin resistance in type 2 diabetic patients. Therefore, it is suggested that there may be a physiological relationship between controlling periodontal infection and diabetes mellitus. Nutritional factors (such as anti-inflammatory 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 (20,32). A study conducted by Sun *et al.* (2011) showed that treatment of periodontal disease in patients with diabetes led to controlling the blood sugar levels and a significant reduction in insulin resistance (33), which is in agreement with the findings of the present study. There are also other studies showing an improvement in blood sugar level after periodontal treatment (34,35). Since lipopolysaccharide 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 (5, 36). In agreement with our study, Brasnyo *et al*. showed that a four-week consumption of resveratrol significantly reduced insulin resistance in patients with type 2 diabetes (24). Mendez-del found that resveratrol supplementation in patients with metabolic syndrome resulted in a significant decrease in blood insulin area under the curve (AUC) but no significant change was seen in the curve for

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glucose level (37). Furthermore, one study by Crandall *et al*. showed that a four- week consumption of resveratrol supplement in patients with impaired glucose tolerance (IGT) improved insulin sensitivity and factors related to blood sugar after a meal, without a significant decrease in FBS (38). 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 in FBS after periodontal treatment in diabetic patients (39). Also, in a study by Debora *et al.*, non-surgical periodontal treatment did not have a significant impact on glycemic control and FBS (40), which is consistent with our study. It is suggested that the beneficial effects of resveratrol are related to inactivation of NF/KB stimulated by bacterial lipopolysaccharide in inflamed tissue and activation of SIRT and AMP kinase (31). Periodontal disease is an inflammatory process in which the leukocytes penetrate into the endothelium of inflamed periodontal tissues. It is believed that the main factor influencing inflammation is infection with oral pathogens. Bacterial Lipo-polysaccharides (LPS) induce the adhesion of leukocytes in periodontal tissue endothelium through the sticky molecules. Resveratrol significantly inhibited the bacterial lipo-polysaccharides. The main mechanism suggested for inhibition of LPS by resveratrol is non-activation of the nuclear factor of KB (NF/KB) (26). Sirtuin proteins (SIRT) are thought to improve mitochondrial function and energy limiting, there is a direct relationship between SIRT and the beneficial role of resveratrol including the improvement of glucose metabolism and insulin sensitivity. AMP 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 (21, 41). 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 effect of glibenclamide) (42). In Bhatt *et al.'s* study, receiving resveratrol supplementation in patients with diabetes mellitus for three months significantly reduced fasting plasma glucose and other risk factors related to glycemic control (27). 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 (30*)*. These studies are inconsistent with the findings of the present study. Probably the length of intervention period in Bhatt's study and healthy subjects in Timmers's study may lead to such diversity in the FBS results. Therefore, further studies with longer duration of treatment 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 (43). Also, in patients with diabetes mellitus and periodontal disease, there may be an increase in some inflammatory factors such as IL6 and TNFα that results in dyslipidemia and hypertriglyceridemia (44, 45). 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 triglycerides (14). In a study conducted by Mointaghavi *et al.*, no significant decrease was observed in serum TG in diabetic patients after periodontal treatment (34). Furthermore, in a study by Crandall *et al.*, no changes were observed in lipid profile including blood triglycerides (38). In the other study by Morten *et al.* in 2013 investigating the effect of receiving resveratrol supplements in healthy obese men, no significant changes were observed in lipid profile (46); these results are consistent with our study. Microorganisms associated with periodontal disease and host response to these microorganisms increase the production of inflammatory factors including IL6, TNFα and IL1B. These inflammatory markers are also involved in insulin resistance (45). In 2014, Nefumi *et al.* evaluated the effects of three weeks resveratrol supplementation on male Wistar rats with periodontal disease and observed an improvement in the inflammatory markers including IL6 and TNFα and a reduction in oxidative stress (47). In another study conducted by Rizzo *et al.*, the effect of resveratrol supplementation and regulation of cytokine production on human periodontal ligament cells was investigated but no significant decrease was seen in the level of pre-inflammatory cytokines including IL1B, IL6 and TNFα (19). The results of these studies are inconsistent with our study. Moreover, in a study

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by Ghanim *et al.*, after a six- week consumption of Polygonum cuspidatum containing resveratrol, a reduction was observed in the inflammatory markers of IL6, TNFα and CRP in healthy individuals (48). Tomé-Carneiro *et al.* also investigated the effect of one year enriched grape extract supplementation containing resveratrol on diabetic patients with hypertension and observed only a significant decrease in the serum levels of IL6 (49). This study is not consistent with the study conducted by Ghanim and Tomé-Carneiro. The duration of the intervention was greater than that of our study. In Morten's study, no significant reduction was observed in TNFα in healthy people after four weeks consumption of resveratrol supplementation (46). In a study by Chen *et al.*, no significant reduction was observed in TNFα after periodontal treatments in patients with type 2 diabetes (39). Similarly, in our study, we found no significant reduction in TNFα after four weeks consumption of resveratrol supplementation.

The link between various nutrients and systemic diseases has been established; however, relatively little work has been done in relating oral conditions with nutrition. Furthermore, to our knowledge, few studies have so far been conducted on the effects of nutritional intervention in adjunction with the non-surgical periodontal treatment 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 pocket depth post-intervention. To the best of our knowledge, there is 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 (47). In a laboratory study in Korea, Joo Park *et al.* (2009) investigated the effect of resveratrol on lipopolysaccharide *P. gingivalis*, and suggested that resveratrol supplementation may help to remove periodontal pathogens (26).

There are some studies showing the beneficial effects of antioxidant or anti-inflammatory nutritional factors such as vitamin c, alpha-tocopherol, beta-carotene, Q10, omega 3, green tea, probiotics and cranberry juice on periodontal status (50) Munozca *et al.* showed that receiving multi-vitamin nutritional supplement in periodontal patients resulted in a significant improvement in periodontal indices, especifically in pocket depth (51). Similarly, in a study by HeshamEl-Sharkawy *et al.*, n-3 PUFA supplementation led to a significant decrease in pocket depth (52).

Conclusion: In the present study, resveratrol supplementation improved insulin resistance and periodontal status in diabetic patients with periodontal disease after four weeks. It is suggested that using resveratrol as a dietary supplement with anti-inflammatory and anti-bacterial properties in adjunction with non-surgical periodontal treatments may be helpful in controlling the periodontal status followed by controlling some complications in diabetes mellitus. Therefore,it is suggested that using resveratrol supplementation and foods rich in resveratrol may be beneficial in diabetic patients with periodontal disease.

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