Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 2769–2774

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Impact of resveratrol supplementation on inflammatory, antioxidant, and periodontal markers in type 2 diabetic patients with chronic periodontitis

Ahmad Zare Javid [a, b], Razie Hormoznejad [c, *], Hojat allah Yousefimanesh [d], Mohammad Hosein Haghighi-zadeh [e], Mehrnoosh Zakerkish [f]

[a] Nutrition and Metabolic Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[b] Department of Nutrition, School of Allied Medical Sciences, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[c] Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[d] Department of Periodontology, School of Dentistry, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[e] School of Public Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[f] Health research institute, Diabetes research center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

ARTICLE INFO

Article history:
Received 29 June 2019
Accepted 23 July 2019

Keywords:
Type 2 diabetes mellitus
Periodontal disease
Resveratrol
Antioxidant
Inflammation

ABSTRACT

Background: Diabetes mellitus and periodontal disease are two common and chronic diseases with bidirectional relationship influence public health and quality of life. The aims of this study was to study the impact of resveratrol supplementation in adjunct with non-surgical periodontal therapy on inflammatory, antioxidant, and periodontal markers in patients with type 2 diabetes with periodontal disease.

Materials and methods: In this randomized clinical trial, 43 patients with diabetes and chronic periodontitis were randomly allocated into two intervention and control groups receiving either resveratrol supplements or placebo for 4 weeks. Serum levels of interleukin 6 (IL6), tumor necrosis factor α (TNFα), total antioxidant capacity (TAC) and clinical attachment loss (CAL) as the main index of periodontal marker were measured pre-intervention and post-intervention.

Results: In the intervention group, the mean serum level of IL6 was reduced significantly ($P = 0.039$) post-intervention (2.19 ± 1.09 and 1.58 ± 1.06). No significant differences were seen in the mean levels of IL6, TNFα, TAC and CAL between two groups post-intervention.

Conclusions: It is suggested that daily consumption of resveratrol supplement may not change TNFα, TAC and CAL, but it would be beneficial in reducing serum levels of IL6. Therefore, further studies are suggested to investigate the effects of resveratrol supplementation along with NST on periodontal status.

1. Introduction

The associations found recently between systemic diseases and oral health indicate that the strategies to improve oral health may increase health outcomes [1]. Diabetes mellitus (DM) is known as a systemic disease and can affect the quality of life and public health. It is associated with a high risk of complications including macrovascular disease, micro-angiopathy, neuropathy, nephropathy, and delayed wound healing. Periodontitis is considered as the sixth diabetic complication. There is a two-way relationship suggested between diabetes mellitus and periodontal disease, so that periodontal disease may increase the risk of diabetes mellitus, and vice versa [2]. Periodontal disease is a chronic infectious disease and cause the destruction of tissue surrounding teeth, formation of periodontal pocket, gingival bleeding and tooth loss [3]. Gram-negative anaerobic bacteria *A. actinomycetemcomitans* (Aa) and *P. gingivalis* (Pg) are considered as the main causative factors of periodontal disease. In addition to these primary factors, the abnormal responses of the host to these bacteria and their products may cause more infection [4]. About 48% of American adults and the same or greater proportions of the other populations are

* Corresponding author. Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Khuzestan, Iran.
E-mail addresses: r_hormozi68@yahoo.com, Hormozi.r@ajums.ac.ir (R. Hormoznejad).

https://doi.org/10.1016/j.dsx.2019.07.042
1871-4021/

infected to periodontal disease [5]. There are some evidence indicate that patients with type 2 DM who are also suffer from periodontitis have a high serum levels of oxidative stress and inflammatory markers such as IL6, TNF α and IL-1B [6]. The high serum and salvia levels of oxidative stress in periodontal patients may disrupt the serum antioxidant capacity [4]. The serum concentration of major antioxidants such as carotenoids, ascorbic acid and bilirubin is decreased in periodontal patients [7,8]. There are several approaches used in the treatment procedure of periodontal disease of which using antibiotics is a common method. However, the frequent use of antibiotics may increase the bacterial resistance [9]. Moreover, "medical nutrition therapy" is considered as a safest complementary approach in the prevention and treatment of periodontal disease. Foods and dietary components with strong anti-inflammatory, anti-microbial and antioxidant properties may be used as suitable and beneficial complementary treatment strategy in adjunct with the other periodontal treatments in periodontal patients [10]. Resveratrol (3, 5, 4′-trihydroxystilbene), which is a polyphenol compound, is found mainly in grapes skin. It is also available in cranberry, blueberry, pistachios and peanuts. The polygonum cuspidatum is known as the richest source of this component. Traditionally, polygonum cuspidatum roots have been used as medicine in China and Japan [11]. Resveratrol can reduce the oxidative stress and apoptosis. It is also known as an anti-inflammatory, anti-tumor, anti-carcinogenic, ant-aging and anti-microbial agent [12]. Resveratrol may reduce the pro-inflammatory cytokines such as IL6, IL-1B, IL8, IL12 and TNF. These inflammatory markers have adverse effects on glucose and lipid metabolism [13]. It is suggested that resveratrol may reduce the oxidative stress through several mechanisms. It eliminates reactive oxygen species (ROS), increases the metabolizing enzymes of ROS such as catalase, superoxide dismutase and glutathione transferase and also, reduces the activity of enzymes involved in the production of ROS [14]. There are few in vitro studies to show that resveratrol may improve the antioxidant defense capacity and systemic inflammation in periodontal ligament cells [12,15]. In addition, it was reported that resveratrol intake reduced plasma lipid, free fatty acids and blood glucose in diabetic patients [16]. Nutrition is considered as an important factor associated with systemic diseases. Many studies have been carried out on the relationship between nutrition and systemic diseases, however, there are few studies on the relationship between nutrition and oral health [10]. Also, there are only a few studies conducted on the impact of dietary supplements in adjunct with other periodontal treatments on periodontal status [12,13,15]. Therefore, in the present study we investigated the effects of resveratrol supplementation in adjunct with non-surgical periodontal therapy on inflammatory, antioxidant, and periodontal markers in diabetic patients with chronic periodontitis.

2. Material and methods

2.1. Subjects and study design

In this randomized double-blind and placebo-controlled clinical trial, the diabetic patients with primary symptoms of chronic periodontitis who were recruited from Ahvaz Golestan hospital, were referred to the dental clinic (in Ahvaz Jundishapur University of Medical Sciences, Iran) for further confirmation of periodontal disease. Totally, 50 diabetic patients with chronic periodontal disease were recruited. A signed consent form was collected from all subjects. The recruited subjects were randomly allocated into control ($n = 25$) and intervention ($n = 25$) groups based on the block design. The inclusion criteria were as: subjects with known type 2 diabetes mellitus (no more than 5 years since diagnosis) and *chronic periodontal disease*, aged between 30 and 60 years, both gender, body mass index (BMI) between 18.5 and 30 kg/m^2 and fasting blood glucose (FBS) lower than 22 mmol/L. The exclusion criteria were as: pregnancy, breastfeeding, smoking, having type 1 diabetes mellitus; using insulin; suffering from any complications of diabetes mellitus such as kidney failure, using immunosuppressive medications, treatment history of periodontal disease during the last six months, using any antioxidant supplement, following any specific diets beyond their usual diets during the last six months.

Subjects in the intervention and control groups received either 480 mg/d resveratrol or placebo capsules (2 pills) along with the non-surgical periodontal therapy (NST) for 4 weeks. Resveratrol capsules were purchased from *Herbafit* company. Each resveratrol capsule provided 480 mg Polygonum Cuspidatum containing 240 mg resveratrol. The resveratrol capsules contained Polygonum Cuspidatum extract (72%), microcrystalline cellulose (filler), gelatin and magnesium stearate. Placebo capsules contained 480 mg starch. The non-surgical treatment was provided for all patients during the intervention period. It comprised the instructions on dental hygiene (such as advising how to brush and to use mouthwash and dental floss correctly), removing dental plaque, scaling and root planning of supragingival using ultrasonic Gracey curettes and scalers (at sites with the probing depth greater than 4 mm). All patients were allowed to use any usual prescribed oral hypoglycemic treatment. The compliance of subjects in this study was double checked through counting the remaining capsules and contacting with telephone. All patients were called three times a week by telephone during the study. For nutritional assessments, a 24-h dietary recall was obtained at baseline and at the end of the study. The dietary intakes of energy, macronutrients, and micronutrients was analyzed using a software called "Nutritionist 4". This clinical trial study was registered in the "Iranian Registry of Clinical Trials" with the IRCT number of 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).

2.2. Biochemical and clinical measurements

A fasting blood sample (5 ml) was collected from subjects at baseline and the end of intervention. Blood samples were centrifuged at 3000 rpm for 5 min and then the supernates were stored at −70 °C until analysis. The serum samples were used to analysis IL6, TNFα and TAC. Serum levels of IL6, TNFα and TAC were measured using *ELISA* method by laboratory kits (eBioscience, Germany for IL6 and TNFα; and LDN, PLabor Diagnostika Nord GmbH, Germany for TAC).

Periodontal status was evaluated in this study by probing depth (PD) and CAL (clinical attachment loss) which are the main periodontal indices. PD and CAL were evaluated by a University of North Carolina No. 15 (a UNC-15) manual periodontal probe and measured at six sites of a tooth (midbuccal, mesiobuccal, mesiolingual, distobuccal, distolingual, and midlingual sites). The CAL and PD were determined by measuring the distance from the cement–enamel junction to the bottom of the pocket/sulcus and evaluated using the distance between free gingival margin and the base of the pocket/sulcus, respectively [16].

2.3. Statistical analysis

Considering 95% confidence with an estimated standard deviation and difference of HOMA-IR [17] as the primary outcome, the sample size was calculated and 20 subjects in each group were determined. Regarding with a possible withdrawal of subjects during the study, 25 subjects were considered in each group. The

statistical analyses were performed using SPSS (version 19). The results presented as mean ± SD. Differences were considered as significant if the P-value was lower than 0.05. The Kolmogorov-Smirnov test was used to assess the normal distribution of variables. The Paired sample *t*-test was used to compare the results within groups and the independent sample *t*-test was used to compare the results between groups.

3. Results

Fig. 1 shows the flow chart of this study. Totally 50 patients were recruited of whom 43 subjects (n = 21 subjects received resveratrol and n = 22 subjects received placebo capsules) completed the study. The compliance procedure showed that 7 subjects did not used the capsules regularly and therefore were excluded. The characteristics of subjects are shown in Table 1. No significant differences were seen between two groups in the mean IL6, TNFα and CAL at baseline. However, a significant difference was observed in TAC between two groups at baseline (Table 1). The other data of the demographic characteristics of subjects were presented in the previous study [18]. Moreover, there were no significant differences seen between two groups for micronutrients with antioxidant properties including vitamins A, C, E, beta-carotene, α-tocopherol, and selenium at baseline and end of the study (The data are available in our pervious study [18]). Table 2 shows the biochemical and clinical parameters at baseline and post intervention in two groups. IL6 levels statistically (P = 0.03) decreased in the intervention group (1.58 ± 1.06 and 2.19 ± 1.09 respectively), but no significant (P = 0.3) difference was detected in the mean levels of IL6 between two intervention and control groups (1.58 ± 1.06 and 1.85 ± 0.59 respectively) post intervention. Regarding with the serum levels of TNFα, the change was not significant (P = 0.25) between intervention and control groups (10.33 ± 0.66 and 10.57 ± 0.68 respectively). Also both within intervention and control groups, there were no significant changes in the mean levels of TNFα post intervention compared with baseline. Regarding with serum levels of TAC, there was no significant (0.05) difference between intervention and control groups (1.35 ± 0.62 and 1.02 ± 0.43) post intervention. No significant changes were also seen in the mean serum levels of TAC in intervention and control groups post intervention. Regarding with CAL, there was no significant (0.06) difference shown between intervention and control groups (2 ± 0.4 and 2.2 ± 0.5) post intervention. However, the CAL was significantly

Table 1
Baseline characteristics of the subjects.

P-value	Intervention group (n = 21)	Control group (n = 22)	varieble
0.71	2.19 ± 1	2.08 ± 0.8	IL-6 (pg/ml)
0.6	10.49 ± 0.47	10.56 ± 0.6	TNF-α (pg/ml)
0.03	1.08 ± 0.37	0.81 ± 0.42	TAC (mmol/L)
0.05	2.35 ± 0.6	2.72 ± 0.5	CAL(mm)

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.

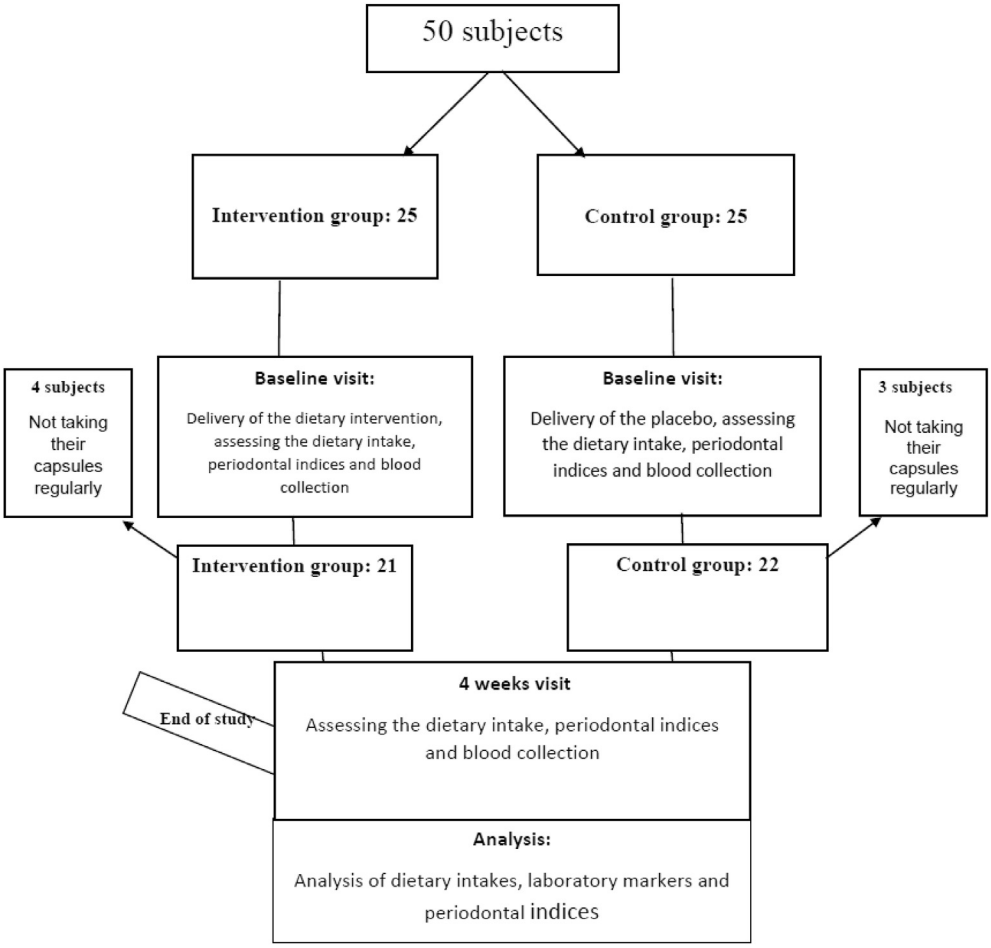

Fig. 1. Flowchart of the study design.

Table 2
Biochemical and clinical variables at baseline and post intervention.

P-value **	Intervention group (n = 21)			Control group (n = 22)			variable
	P-value *	After 4 weeks	Baseline	*P-value* *	After 4 weeks	Baseline	
0.3	0.039	1.58 ± 1.06	2.19 ± 1.09	0.1	1.85 ± 0.59	2.08 ± 0.82	**IL-6 (pg/ml)**
0.25	0.2	10.33 ± 0.66	10.49 ± 0.47	0.93	10.57 ± 0.68	10.56 ± 0.61	**TNF-α (pg/ml)**
0.05†	0.1	1.35 ± 0.62	1.08 ± 0.37	0.08	1.02 ± 0.43	0.81 ± 0.42	**TAC** (mmol/L)
0.06	0.002	2 ± 0.4	2.35 ± 0.6	0.001	2.2 ± 0.5	2.72 ± 0.5	**CAL(mm)**

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.
†P < 0.05 was considered as significant using univariate analysis variance test.

reduced in both intervention and control groups post intervention.

4. Discussion

In this study on diabetic patients with periodontal disease, we found that receiving resveratrol supplementation for four weeks may not change TNFα, TAC and CAL, but it would be beneficial in serum levels of IL6. Recently, herbal medicine is used for the treatment and prevention of periodontitis. Polyphenolic compounds are considered as potential agents capable of reversing, retarding and inhibiting the progression of all disorders caused by inflammation and oxidative stress [9,19–21]. Resveratrol as a natural polyphenol may reduce the inflammation and oxidative stress. In addition, Resveratrol play a significant antimicrobial role against the periodontal pathogens *A. actinomycetemcomitans* (Aa) and *P. gingivalis* (Pg). These microorganisms are involved in the etiology of periodontal disease and the host response to these microorganisms may increase the production of inflammatory markers including IL6, TNFα and IL1B. These inflammatory markers disrupt lipid and glucose metabolism and are also involved in insulin resistance [21]. IL6 may induce the osteoclast formation and consequently promote bone resorption. *P. gingivalis* as a key factor in the etiology of periodontitis can increase the secretion of IL6 and is associated with hard-tissue destruction. Resveratrol may activate osteoblastogenesis and lead to formation of new bone and delay osteoblastogenesis. These properties may be very important in the treatment of periodontitis [22]. Naofumi et al. investigated the effects of resveratrol on periodontal status in Wistar male rats and found the beneficial effects of resveratrol on bone loss [15]. Furthermore, Matsuda et al. investigated the effects of resveratrol on bone loss in mice and observed that resveratrol suppressed the alveolar bone resorption by disrupting the osteoclast differentiation [23]. Moreover, in a study carried out by Ornstrup et al. the effects of a high-dose resveratrol supplementation were investigated on bone in men with metabolic syndrome and it was shown that resveratrol affects positively on bone by stimulating the mineralization or formation. It is suggested that the reduction in IL6 levels observed in our study may be involved in improvement of bone resorption and the infection occurred in periodontal disease [24]. In 2014, Tamki et al. evaluated the effects of resveratrol supplementation on periodontal status in Wistar rats and detected an improvement in serum levels of IL6 and TNFα [15]. In another study carried out by Rizzo et al., the effect of resveratrol extract on human periodontal ligament cells was assessed, but no significant decrease was observed in the serum levels of IL1B, IL6 and TNFα [13]. The results of these studies are not concur with present study. Moreover, in a study by Ghanim et al. following a consumption of *Polygonum cuspidatum* (source of resveratrol), a reduction was detected in inflammatory markers including IL6, TNFα and CRP in healthy individuals [25]. *Tomé-Carneiro* et al. also assessed the effects of 12 months of resveratrol supplementation on diabetic patients with hypertension and observed only a statistically significant decrease in the mean serum levels of IL6 [26]. This study was not consistent with the studies carried out by Ghanim and *Tomé-Carneiro*. The duration of resveratrol supplementation in these trials was greater than that of present study. In a study by Morten's, no significant reduction was detected in TNFα in healthy subjects after 4 weeks ingestion of resveratrol supplement [27]. Similarly in Chen's study, no significant reduction was seen in TNFα after periodontal therapy in diabetic patients [28]. In present study, we also found no significant reduction in serum levels of TNFα following 4 weeks ingestion of resveratrol supplement. An increase in oxidative stress may play an important role in the progression of several diseases including diabetes mellitus, cardiovascular diseases, liver diseases, and periodontitis. In addition, oxidative stress can interprete the relationship between systemic conditions and periodontal disease [4]. Resveratrol is a known scavenger of hydroxyl radicals, superoxide, and peroxynitrite. Resveratrol as a scavenger of ROS, increases mitochondrial biogenesis via activation of AMP-activated protein kinase (AMPK) and sirtuin 1 (Sirt1). The ROS includes hydroxyl, nitric oxide radical species, superoxide, and non-radical derivatives of oxygen. Resveratrol can also activate the antioxidant defense pathway through the nuclear factor 2 (Nrf2). Nrf2 is considered as an important sensor of oxidants and toxic xenobiotic substances. Furthermore, resveratrol reduces nitric oxide (NO) expression which may collaborate with the reduction of oxidative status. Several effects of resveratrol, N-acetylcysteine (NAC), and quercetin on human gingival fibroblasts under oxidative stress indicated that resveratrol is the most effective agent for inhibition of ROS production [29]. In a study by Apostolidou et al. after four weeks consumption of resveratrol, no significant reduction was observed in TAC in patients with asymptomatic hypercholesterolemic (AHC)., However, a significant reduction was observed in normocholesterolemics (NCs) individuals [30]. Similarly, in a study by Ghanim et al. a significant reduction was observed in TAC in healthy subjects with a high fat meal post resveratrol supplementation [31]. The findings of these two studies indicate that resveratrol supplementation may improve TAC in healthy human subjects, but not in patients. Similarly, in our study, we found no significant decrease in TAC following four weeks consumption of resveratrol in diabetic patients with periodontitis. Few studies investigated the effects of resveratrol supplementation on TAC status. Therefore, further studies in this regard are required. In a study by Zare Javid et al. the effects of a customized dietary intervention on TAC for 3 and 6 months was investigated in subjects with adult periodontitis and it was found that TAC was increased post intervention [32]. In this study the duration of the intervention was greater than that of present study. Nutritional compounds with antioxidant properties are implicated in systemic and oral diseases which may be linked to obesity, dyslipidemia and hypertension. There is an increasing interest in the links between health benefits of nutritional compounds such as nuts, berries, complex

carbohydrate, unsaturated fats, vitamin B, D antioxidants and cardiovascular diseases, diabetes mellitus and periodontitis. In our pervious study resveratrol supplementation in adjunct with other periodontal treatments improved insulin resistance and pocket depth (PD) in diabetic patients with periodontal disease [18]. In the present study, we reported CAL as a marker of periodontal status. The non-surgical periodontal therapy was performed for all subjects in both intervention and control groups. There was an improvement in CAL in both groups at the end of the study, however, resveratrol supplementation alone did not significantly improve periodontal status. There is no human study investigating the effects of resveratrol supplementation on CAL. In a study by Machida et al. the relationship between plasma reactive oxygen metabolites (ROM) and periodontal condition was assessed. It was shown that increase in plasma ROM was associated with those in CAL in periodontal patients. It was suggested that periodontal treatment decreases ROM levels and increases TAC [4]. In another study by Iwasaki et al. the relationship between serum antioxidants including α tocopherol, ascorbic acid and CAL was evaluated in Japanese subjects. It was found that low levels of α tocopherol are associated with increased periodontal disease [33]. Moreover, in a study conducted by Iwasaki et al., the relationship between saturated fatty acids (SFAs) and CAL was investigated. They reported that high intake of SFA associated with periodontal disease [34].

5. Conclusion

The present study show that daily resveratrol supplementation (as a nutritional factor in adjunction with NST) may not change TNFα, TAC and CAL, but it would be beneficial in improvement serum levels of IL6 in diabetic patients with periodontal disease. A bidirectional relationship between diabetes and periodontitis may be mediated by several inflammatory markers which may reduce in response to common treatment. In addition, genetics, epigenetics, susceptibility, response and environmental factors are some contributing factors interfere with such results. Therefore, further studies are suggested to investigate the effects of antioxidant supplementation along with NST on periodontal status.

Conflicts of interest

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

Acknowledgements

This study is part of M.Sc thesis of MS Hormoznejad. This work was financially supported by a grant (NRC-9304) from Vice-Chancellor for Research Affairs of Ahvaz Jundishapur University of Medical Sciences. The authors express thanks for the Nutrition and Metabolic Disorders Research Center, and Research Center for Diabetes, Endocrinology and Metabolism clinic employees of Ahvaz University Golestan Hospital and Dental Clinic of Ahvaz Jundishapur University of Medical Sciences.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.07.042.

References

[1] Ritchie CS, Joshipura K, Hung H-C, Douglass CW. Nutrition as a mediator in the relation between oral and systemic disease: associations between specific measures of adult oral health and nutrition outcomes. Crit Rev Oral Biol Med 2002;13(3):291–300.
[2] Grover HS, Luthra S. Molecular mechanisms involved in the bidirectional relationship between diabetes mellitus and periodontal disease. J Indian Soc Periodontol 2013;17(3):292.
[3] Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol 1999;4(1):1–6.
[4] Machida T, Tomofuji T, Ekuni D, et al. Longitudinal relationship between plasma reactive oxygen metabolites and periodontal condition in the maintenance phase of periodontal treatment. Dis Markers 2014;2014.
[5] Albandar JM. Epidemiology and risk factors of periodontal diseases. Dent Clin 2005;49(3):517–32.
[6] Bastos AS, Graves DT, Loureiro APdM, et al. Lipid peroxidation is associated with the severity of periodontal disease and local inflammatory markers in patients with type 2 diabetes. Int J Clin Endocrinol Metab 2012;97(8):E1353–62.
[7] Sree SL, Sethupathy S. Evaluation of the efficacy of taurine as an antioxidant in the management of patients with chronic periodontitis. Dent Res J 2014;11(2):228.
[8] Diab-Ladki R, Pellat B, Chahine R. Decrease in the total antioxidant activity of saliva in patients with periodontal diseases. Clin Oral Investig 2003;7(2):103–7.
[9] O'connor D, Wong R, Rabie A. Resveratrol inhibits periodontal pathogens in vitro. Phytother Res 2011;25(11):1727–31.
[10] Soory M. Inflammatory mechanisms and redox status in periodontal and cardiometabolic diseases: effects of adjunctive nutritional antioxidants and statins. Infect Disord - Drug Targets 2012;12(4):301–15.
[11] Szkudelska K, Szkudelski T. Resveratrol, obesity and diabetes. Eur J Pharmacol 2010;635(1–3):1–8.
[12] Park H-J, Jeong S-K, Kim S-R, et al. Resveratrol inhibits Porphyromonas gingivalis lipopolysaccharide-induced endothelial adhesion molecule expression by suppressing NF-κB activation. Arch Pharm Res 2009;32(4):583–91.
[13] Rizzo A, Bevilacqua N, Guida L, Annunziata M, Carratelli CR, Paolillo R. Effect of resveratrol and modulation of cytokine production on human periodontal ligament cells. Cytokine 2012;60(1):197–204.
[14] Carrizzo A, Forte M, Damato A, et al. Antioxidant effects of resveratrol in cardiovascular, cerebral and metabolic diseases. Food Chem Toxicol 2013;61:215–26.
[15] Tamaki N, Orihuela-Campos RC, Inagaki Y, Fukui M, Nagata T, Ito H-O. Resveratrol improves oxidative stress and prevents the progression of periodontitis via the activation of the Sirt1/AMPK and the Nrf2/antioxidant defense pathways in a rat periodontitis model. Free Radic Biol Med 2014;75:222–9.
[16] Liu K, Zhou R, Wang B, Mi M-T. Effect of resveratrol on glucose control and insulin sensitivity: a meta-analysis of 11 randomized controlled trials–. Am J Clin Nutr 2014;99(6):1510–9.
[17] Brasnyo P, Molnar GA, Mohas M, et al. Resveratrol improves insulin sensitivity, reduces oxidative stress and activates the Akt pathway in type 2 diabetic patients. Br J Nutr 2011;106(3):383–9.
[18] Zare Javid A, Hormoznejad R, Zakerkish M, Haghighi-zadeh MH, Dehghan P, Ravanbakhsh M. The impact of resveratrol supplementation on blood glucose, insulin, insulin resistance, triglyceride, and periodontal markers in type 2 diabetic patients with chronic periodontitis. Pharmacogn Res 2017;31(1):108–14.
[19] Zare Javid A, Maghsoumi-Norouzabad L, Ashrafzadeh E, et al. Impact of cranberry juice enriched with omega-3 fatty acids adjunct with nonsurgical periodontal treatment on metabolic control and periodontal status in type 2 patients with diabetes with periodontal disease. J Am Coll Nutr 2018;37(1).71-9.
[20] Babaei H, Forouzandeh F, Maghsoumi-Norouzabad L, Yousefimanesh HA, Ravanbakhsh M, Zare Javid A. Effects of chicory leaf extract on serum oxidative stress markers, lipid profile and periodontal status in patients with chronic periodontitis. J Am Coll Nutr 2018;37(6):479–86.
[21] Wu Y-Y, Xiao E, Graves DT. Diabetes mellitus related bone metabolism and periodontal disease. Int J Oral Sci 2015;7(2):63.
[22] Varela-López A, Bullón P, Giampieri F, Quiles JL. Non-nutrient, naturally occurring phenolic compounds with antioxidant activity for the prevention and treatment of periodontal diseases. Antioxidants 2015;4(3):447–81.
[23] Matsuda Y, Minagawa T, Okui T, Yamazaki K. Resveratrol suppresses the alveolar bone resorption induced by artificial trauma from occlusion in mice. J Oral Dis 2017;24(3):412–21.
[24] Ornstrup MJ, Harsløf T, Kjær TN, Langdahl BL, Pedersen SB. Resveratrol increases bone mineral density and bone alkaline phosphatase in obese men: a randomized placebo-controlled trial. Int J Clin Endocrinol Metab 2014;99(12):4720–9.
[25] Ghanim H, Sia CL, Abuaysheh S, Korzeniewski K, et al. An antiinflammatory and reactive oxygen species suppressive effects of an extract of Polygonum cuspidatum containing resveratrol. Int J Clin Endocrinol Metab 2010;95(9):E1–8.
[26] Tomé-Carneiro J, Larrosa M, Yánez-Gascón MJ, et al. One-year supplementation with a grape extract containing resveratrol modulates inflammatory-related microRNAs and cytokines expression in peripheral blood mononuclear cells of type 2 diabetes and hypertensive patients with coronary artery disease. Pharmacogn Res 2013;72:69–82.
[27] Poulsen MM, Vestergaard PF, Clasen BF, et al. High-dose resveratrol supplementation in obese men: an investigator-initiated, randomized, placebo-controlled clinical trial of substrate metabolism, insulin sensitivity, and body composition. Diabetes 2013;62(4):1186–95.

[28] Chen L, Luo G, Xuan D, Wei B, Liu F, Li J, et al. Effects of non-surgical periodontal treatment on clinical response, serum inflammatory parameters, and metabolic control in patients with type 2 diabetes: a randomized study. J Periodontol 2012;83(4):435–43.
[29] Orihuela-Campos RC, Tamaki N, Mukai R, et al. Biological impacts of resveratrol, quercetin, and N-acetylcysteine on oxidative stress in human gingival fibroblasts. J Clin Biochem Nutr 2015;56(3):220–7.
[30] Apostolidou C, Adamopoulos K, Iliadis S, Kourtidou-Papadeli C. Alterations of antioxidant status in asymptomatic hypercholesterolemic individuals after resveratrol intake. Int J **Food** Sci Nutr 2016;67(5):541–52.
[31] Ghanim H, Sia CL, Korzeniewski K, Lohano T, et al. A resveratrol and polyphenol preparation suppresses oxidative and inflammatory stress response to a high-fat, high-carbohydrate meal. Int J Clin Endocrinol Metab 2011;96(5):1409–14.
[32] Zare Javid A, Seal C, Heasman P, Moynihan P. Impact of a customised dietary intervention on antioxidant status, dietary intakes and periodontal indices in patients with adult periodontitisJ. Hum Nutr Diet 2014;27(6):523–32.
[33] Iwasaki M, Manz M, Taylor G, Yoshihara A, Miyazaki H. Relations of serum ascorbic acid and α-tocopherol to periodontal disease. J Dent Res 2012;91(2):167–72.
[34] Iwasaki M, Manz M, Moynihan P, et al. Relationship between saturated fatty acids and periodontal disease. J Dent Res 2011;90(7):861–7.