RESEARCH ARTICLE

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Investigating the Extent of mRNAs of the Genes Associated with Apoptosis and *OGG1* in the Gingival Connective Tissue of Patients Suffering from Chronic Periodontitis and Diabetes Mellitus

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Abstract

Objectives: Cellular apoptosis plays a key role in the pathogenesis of periodontal disease. Meanwhile, diabetes mellitus can also promote cellular apoptosis of connective tissues. Abnormalities in the function of 8-oxoguanine DNA glycosylase (*OGG1*) can promote oxidative DNA damage, especially in the mitochondria. This study was performed to investigate expression of the genes associated with apoptosis and *OGG1* in the gingival connective tissue of patients suffering from chronic periodontitis and diabetes mellitus. **Methods:** Forty patients with diabetes and chronic periodontitis along with 20 nondiabetic patients with chronic periodontitis were investigated in this study. Four weeks after scaling and root planning for the treatment of periodontitis, periodontal surgery was performed. The gingival tissues obtained during the surgery were sent to the laboratory in order to investigate the expression of genes associated with apoptosis and *OGG1*. **Results:** The mRNA and protein levels of *caspase 3* and 9 were higher in the patients suffering from both diabetes and periodontitis compared to the nondiabetic chronic periodontitis patients (P<0.001). Furthermore, the expression level of *OGG1* gene was higher in patients with chronic periodontitis and diabetes mellitus compared to the chronic periodontitis nondiabetic patients, though this difference was not significant. **Conclusion:** The expression levels of genes associated with apoptosis and *OGG1* in the gingival connective tissue of diabetic individuals with chronic periodontitis was higher than in nondiabetics with identical periodontal conditions. Thus, the signals and function of the genes examined in this study can be important and useful factor for further investigation in the treatment of patients with both periodontitis and diabetes.

Keywords: *Caspase 3- Caspase 9- OGG1*- Diabetes- Periodontal tissue

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Introduction

Diabetes mellitus refers to elevation of blood glucose levels resulting from impaired insulin secretion, insulin dysfunction, or both [1]. This disease in addition to high prevalence causes various complications in different parts of the body including the oral cavity which can be a major cause of morbidity and mortality among diabetic patients, while also incurring staggering costs to the economy of the society [2]. By developing autonomous neuropathy as well as microvascular and macrovascular complications, diabetes causes changes in different organs of the body [3]. Furthermore, diabetes has a strong impact on production and composition of the saliva, and by changing its pH, it promotes dental caries and plaques [1-4].

Periodontitis is established as an infectious and inflammatory disease and the most important cause of loss of teeth in adults [5]. Various complex inflammatory and immunological processes are involved in progression of periodontitis. The histological activities in the periodontium of the patient include cellular activities with regards to infiltration of inflammatory cells as well as degeneration and regeneration of epithelial and connective tissues [6]. Two cellular processes that are affected by diabetes include inflammation and apoptosis [7]. Apoptosis refers to programmed cell death which is stimulated and initiated by different signals which leads to clear morphological changes in cells [8, 9].

Since apoptosis is responsible for elimination of unwanted, damaged, and infectious cells in the body, recently research related to it has undergone major transformations and advances. Indeed, today impairments in apoptosis in the body (its reduction or enhancement) is being put forward as a new theory in the pathogenesis

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and development of some diseases whose mechanism of development is not fully understood [10, 11].

It seems that existence of proapoptotic and anti-apoptotic factors determines the extent of resistance or susceptibility of cells to apoptosis. These factors play a key role in the development, progression, and chronicity of some degenerative, autoimmune, and malignant diseases. Thus, identification of the factors affecting these factors and ultimately on the apoptosis process can be promising in understanding the unknown aspects of some diseases and in providing novel treatment methods [12, 13]. Following development of apoptosis and elevation of extent of ROS in the host cell, the extent of expression of *OGG1* repair protein grows, whereby *OGG1* prevents from ROS-induced damage through repairing DNA. Mutations in some enzymes involved in base excision repair, such as DNA polymerase and *OGG1*, have been found to bring about significant oxidative damage to mtDNA, which consequently leads to apoptosis [14, 15]. However, it is unclear whether the expression of *OGG1* is involved in the gingival connective tissue of patients suffering from chronic periodontitis and diabetes mellitus.

Although the role of diabetes is established in the pathogenesis of periodontitis [16, 17], molecular studies are still required for investigating the details of the way hyperglycemia and other systemic complications of diabetes affect the pathogenesis of different diseases including periodontitis. Given the emphasis that exists on the role of apoptosis of different immune cells, along with bone and connective tissue in pathogenesis of periodontitis, and considering the effect of hyperglycemia on the apoptosis of cells in different tissues, the present study aims to investigate the level of mRNA of the genes associated with apoptosis and *OGG1* in the gingival connective tissue of patients suffering from chronic periodontitis and diabetes mellitus.

Materials and Methods

Studied patients

In this study, patients referring to dentistry clinic of Tehran City in 2022 were chosen. The patients who had controlled diabetes (Type II) with *HBA1C* lower than 7.5 and FBS lower than 150 were included. These patients were first asked about history of diabetes and their diet by the dentist. In the intraoral examination, the patients were examined in terms of existence of lesions by an oral and maxillofacial specialist. All of the patients included in this study had moderate to severe chronic periodontitis based on the extent of loss of clinical adhesion (3 mm or more). In addition, having at least 14 teeth (except for the third molars) and confirmation of the need to undergo periodontal surgery in the second phase of the treatment after evaluating the results of the first phase of the treatment (at least after four weeks) were among the other inclusion criteria. The exclusion criteria included pregnancy, tobacco smoking, extensive antibiotic consumption over the past two months, history of taking corticosteroids over the past six months, history of periodontal treatment over the past six months, existence of systemic conditions or taking drugs that can interfere in the pathogenesis of periodontal disease or in the course of the treatment, as well as contraindications of periodontal surgery according to the patient's dentist.

For all of the included patients, the first phase of periodontal treatments was performed to resolve inflammation and remove local factors, whereby the methods of oral health maintenance were trained to them completely. After at least four weeks, the periodontal status of the patients was reevaluated. In case the second phase of the periodontal treatment was required, periodontal flap surgery was performed. All of the gingival tissues that would be separated during the periodontal flap surgery (including granulation tissue as well as the area separated by submarginal cuts) were placed inside special sterilized tubes using sterilized tweezers and without getting contaminated with the saliva or mucus of the patient (to prevent mixing with bacterial, fungal RNAs as well as those of exfoliated cells, and other cases), and kept inside fridge. At the end of the surgery, the tubes were collected and after assigning codes to each sample, they were sent to the molecular laboratory as packaged in dry ice to perform qRT-pcr test [18, 19].

RNA extraction

The RNA of all of the obtained gingival tissues was extracted using columnar RNA extraction kit purchased from Yekta Tajhiz Azma Co., Iran, in the molecular laboratory of the University of Tehran. They were then at kept -70°C.

Primary design and analysis of its quality using agarose gel

In the present study, after obtaining the sequence of exons from NCBI and Ensembl databases, the examined primers were designed on two exons as existence of forward or reverse on the binding site of two exons using Beacon Designer software. Next, using Beacon and Oligo software applications plus NCBI database, the blasted primers were investigated in terms of the position, herpin, and additional bond. Thereafter, after ordering and purchasing primers, they were used diluted and used according to the manufacturer's protocol (Table 1).

After analysis of nano drop and agarose gel, by Yektatajhiz Azma kit, it was converted to cDNA. Next, given the binding temperature, the thermal formula of 95°C was used for separating the cDNA strands, for 10 min, followed by a 40-cycle period involving 95°C in 10 s, 60°C in 20 s, 72°C in 20 s it was used for PCR analysis as well as analysis of the quality of the investigated primers in agarose gel 2%.

Real-time and analysis

All of the biological samples were placed inside real-time device (Rotor-Gene Q 2.3.5, Rotorgen Co.) in triplicate. It was used according to the thermal protocol of 95°C for separating cDNA strands, for 10 min, followed by a 40-cycle period involving 95°C in 10 s, 60°C in 20 s, 72°C in 20 s for replication and reading. In this experiment, master mix and cyber green kit (Yekta Tajhiz Azam Co.) was used. First, standard curve was performed for normalization of cDNA. Next, the melting curve and

Table1. List of Different RT-qPCR Primers Used in the Study

Gene (ENST)	Sequence (5' – 3')	Tm (°C)	Length (bp)
Caspase 3	F: ATGGGAGCAAGTCAGTGGAC	60	84
(ENST00000393585.6)	R: CGTACCAGAGCGAGATGACA		
Caspase 9	F: GGCGGAGCTCATGATGTCTGTG	61	156
(ENST00000469637.1)	R: TTCCGGTGTGCCATCTCCATCA		
BCL-2	F: GAGCGTCAACAGGGAGA	60	164
(ENSG00000126453)	R: GCCAGGAGAAATCAAACA		
BAX	F: ACTAAAGTGCCCGAGCTGA	60	161
(ENSG00000087088)	R: ACTCCAGCCACAAAGATGGT		
B-ACTIN	F: CTACCTTCAACTCCATCA	60	165
(ENST00000515712.1)	R: GAGCAATGATCTTGATCTTC		
OGG1	F: ACTGTCACTAGTCTCACCAG	60	156
ENST00000602976.1	R: CCTTCCGGCCCTTTGGAAC		

CT were analyzed in each sample. The initial analysis was performed by GeneX v6.7 software, with all results being calculated in terms of Delta CT and log-two. Next, statistical analysis was performed by GraphPad Prism software (Version 8).

Western

Immunoblot analysis for detection of caspase3, *caspase9, BCL-2, BAX,* and *OGG1* was performed as previously described [20]. Briefly, large intestinal cancerous and non-cancerous tissues (0.1gm) were lysed in 0.9 ml lysis buffer [50 mM Tris-HCl (pH 8.0), 150 mM NaCl, 0.5% Nonidet P-40, 0.5% CHAPS] including 0.1% protease inhibitor cocktail III (Calbiochem, San Diego, CA, USA). The tissue lysates were kept on ice for 30 min and centrifugated at 16,000 ×g for 10 min to remove tissue debris. The total protein level of tissue lysates was measured using the bicinchoninic acid assay (BCA) kit (Thermo Scientific). Samples were separated by 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto polyvinylidene difluoride membranes (PVDF, Roche, Germany). Membranes were then blocked overnight by 5% skimmed milk in TBS 0.1% Tween-20, at 4°C. After incubation of membranes with the primary antibody; primary antibodies included, cleaved caspase-9, cleaved *caspase-3, BCL*, *BAX*. and anti-*GAPDH* [all at a dilution of 1:1000] and anti-rabbit HRP-conjugated secondary antibody (Cell signaling technology, USA) at a dilution of 1:5000. visualization was performed using enhanced CL-based Clarity Western ECL Substrate (Bio-Rad) in combination with an ECL imaging system (Uvitec, Germany). Signals on WB were quantified by Image J 1.42q software (Wayne Rasband, NIH, Bethesda, MA) and the results were eventually normalized to *GAPDH*.

Statistical Analyses

The collected data were analyzed using a t-test. The significance level was 0.0001. All results were presented as mean ± SD. All analyses were carried out using GraphPad Prism 8.

Results

This study was performed on 40 patients (15 males and 25 females) suffering from diabetes and chronic periodontitis with age range 37-64 years along with 20 nondiabetic patients (8 males and 12 females) with chronic periodontitis with age range 40-60 years.

The extent of expression of apoptosis-associated genes

The extent of expression of *caspase 3* and 9 across the mRNA surface was higher in those with chronic periodontitis and diabetes mellitus compared to nondiabetic patients with chronic periodontitis ($P<0.0001$) (Figure 1). The extent of expression of *BCL-2* and *BAX* as well as *BAX/BCL-2* ratio did not show any significant difference (Figure 1).

Furthermore, the extent of expression of *OGG1* gene was higher in those with chronic periodontitis and diabetes mellitus compared to those with chronic periodontitis and without diabetes, though this difference was not significant (Figure 1).

The extent of expression of *caspase 3* and 9 across the protein Levels surface was higher in those with chronic periodontitis and diabetes mellitus compared to nondiabetic patients with chronic periodontitis ($P<0.0001$) (Figure 2). The extent of expression of *BCL-2* and *BAX* as well as *BAX*/*BCL-2* ratio did not show any significant difference (Figure 2).

Discussion

Periodontitis is an inflammatory disease of dental supporting tissues, caused by a special group of microorganisms, leading to extensive degeneration of the periodontal ligament and alveolar bone. The progression rate of this disease can be affected by local factors (affecting plaque accumulation), systemic factors (diabetes mellitus and HIV infection) or environmental factors such as cigarette, toxins, and stress [21]. Diabetes mellitus is a complex metabolic disorder, characterized by chronic hyperglycemia with its major complications being increased susceptibility to infection and poor wound

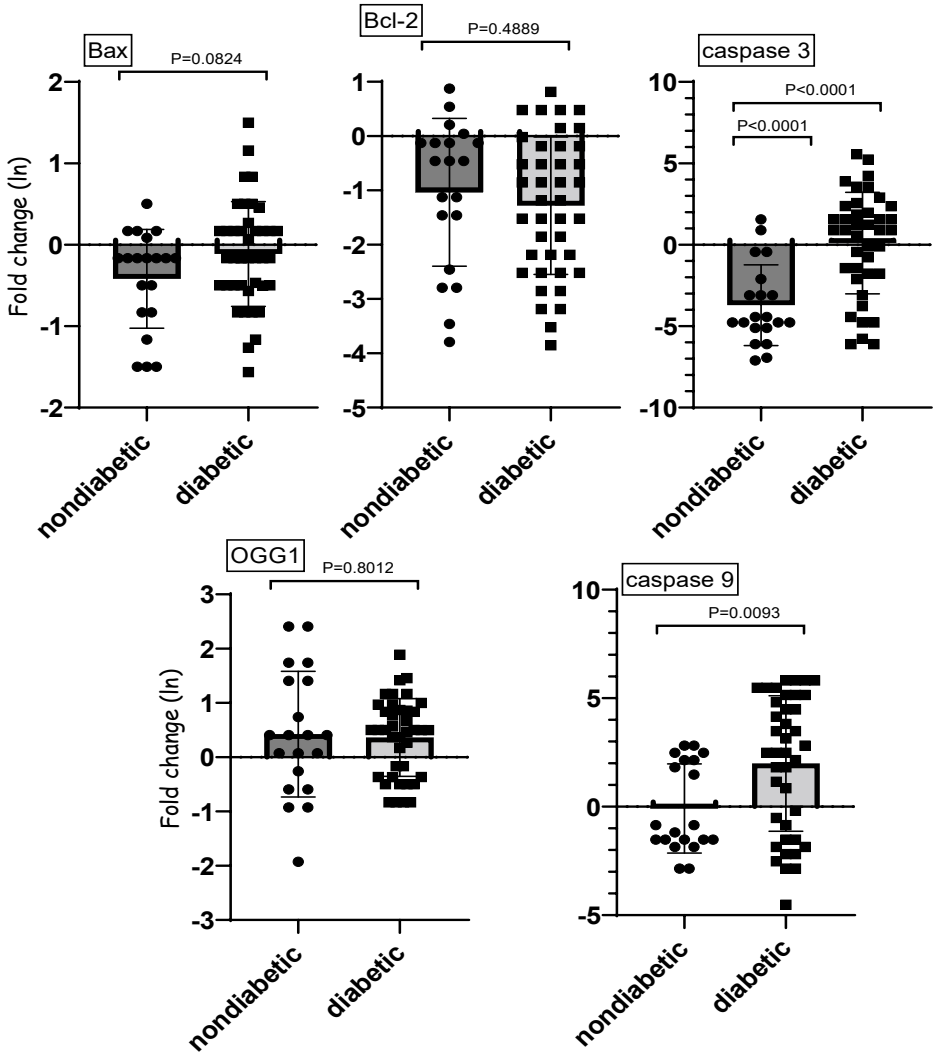

Figure 1. Comparative mRNA Levels Results of *Caspase 3, Caspase 9, BCL-2*, *BAX* and *OGG1* in chronic periodontitis and diabetes mellitus (n= 40), and nondiabetic patients with chronic periodontitis (n=20).

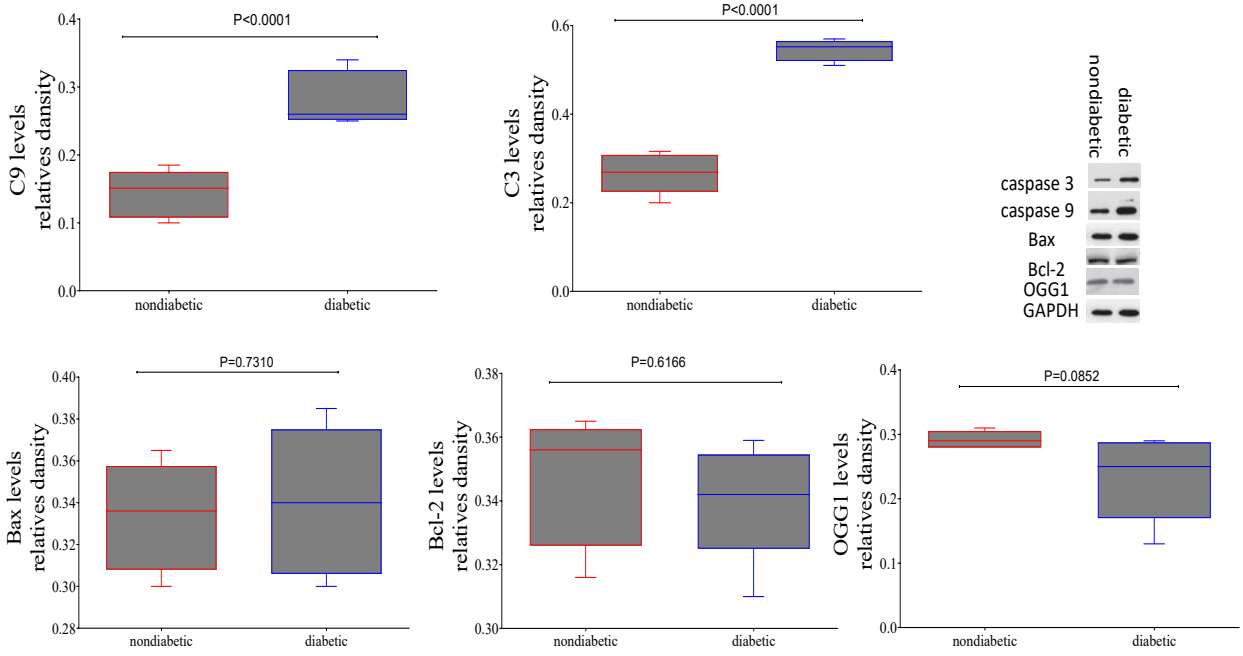

Figure 2. Comparative Protein Levels Results of *Caspase 3, Caspase 9, BCL-2, BAX* and *OGG1* in Chronic Periodontitis and Diabetes Mellitus (n= 40), and Nondiabetic Patients with Chronic Periodontitis (n=20).

healing [22]. Studies in recent years have shown that those with diabetes are three times more at risk of developing periodontitis [23-25]. In another study by Portes et al. [26], they found that diabetes and periodontitis are directly interrelated. The present study results showed that the extent of expression of *caspase 3* and 9 was higher in those with chronic periodontitis plus diabetes as compared to patients with chronic periodontitis but without diabetes. The study by Shoukheba et al. [27] indicated that *caspase 3* grows in the serum level of those with type II diabetes and chronic periodontitis.

In the study by Kubra et al. (2019), examining the role of *caspase 8, caspase 9,* and apoptosis-inducing factor in periodontal disease, it was found that the internal pathway of mitochondrial axis including caspase-9 and AIF, along with the external pathway including caspase-8 are important for development of aggressive and chronic periodontitis [28].

Other results of the present study revealed that the extent of expression of *BCL-2* and *BAX* did not increase in those with chronic periodontitis and diabetes mellitus compared to patients with chronic periodontitis but without diabetes.

In a study by Youmin et al. (2021) on diabetic rats with periodontitis comorbidity, it was found that the diabetic rats showed extensive changes in comparison to the control animals; the level of expression of *BCL-2* showed a significant increase in the diabetic rats compared to control animals [29], which does not concur with the present study results. This can be due to the type of animal and chronicity of periodontitis in the examined patients. However, in the mentioned study, the extent of expression of *BAX* and relationship between *BAX*/*BCL2* did not show any changes and confirmed the obtained results.

Other results of the present study showed higher expression of *OGG1* gene in those with chronic periodontitis and diabetes mellitus compared to those with chronic periodontitis but without diabetes. *OGG1* is one of the essential components of the base excision repair (BER) pathway and is required for elimination of DNA-oxidized guanin nucleotides [30, 31]. The study by Cheng et al. [32] revealed that periodontitis leads to development of apoptosis and *OGG1* finds overexpression in periodontitis compared to the control tissue, and can be used as a biomarker in diagnosis of periodontitis. Regardless, the significant difference in the extent of *OGG1* in those with chronic periodontitis and diabetes mellitus compared to patients with chronic periodontitis but without diabetes may have resulted from relatively small sample size in each of the study groups. The management of diabetes is complex and the prevention of cardiovascular and microvascular disease, through early detection and management of complications, are key components. Lifestyle intervention, education, self-management and self-monitoring are particularly important, in addition to treatments to reduce blood glucose, blood pressure and lipids [33]. Similar to diabetes, current treatment philosophies for periodontitis strongly emphasise self-management through patient education. A supportive and facilitative approach by the dental team is essential, but there must be a clear understanding that patient-performed plaque control is the vehicle by which to control the inflammation which drives periodontal tissue destruction. Structured education programmes are effective in the management of diabetes, and similar programmes are being developed for the management of periodontitis [34].

In conclusion, the expression of *caspase 3* and 9 in the gingival connective tissue showed a significant elevation in diabetic patients with chronic periodontitis compared to their nondiabetic counterparts. This suggests higher extent of apoptosis in this disease. Thus, finding drugs or processes that interfere with the stages of synthesis or function of the mentioned proapoptotic proteins may contribute to improvements in the periodontal disease state and treatment outcomes in patients with diabetes.

Author Contribution Statement

Salmeh Kalbassi, Safa Samadzadeh Etehadi, Mohammadreza Azimi performed the experiments, conceived and designed the study, and wrote, analyzed, funded, and critically revised the manuscript.

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Data Availability

The datasets generated and/or analyzed during the current study are available upon reasonable request from the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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