Relationship between dental caries and saliva’s visfatin levels, total antioxidant capacity (TAC) and total oxidant status (TOS)

Abstract

Objectives: Dental caries is a multifactorial infectious disease caused by the colonization and proliferation of bacteria in the mouth. Recently, it has been reported that local antioxidant and oxidant status may play an important role in the pathogenesis of dental caries. Visfatin is an adipocytokine that enhances leukocyte activation and release of proinflammatory cytokines. In this study, our aim was to investigate the salivary visfatin levels, total antioxidant capacity (TAC), and total oxidant status (TOS) in patients with and without dental caries.

Methods: Saliva samples were collected from 50 caries-free individuals and 115 patients with dental caries who were admitted to Selcuk University Restorative Dentistry Clinics. Saliva samples were collected based on the stimulated saliva collection procedure. Visfatin levels were measured using enzyme-linked immunosorbent assay. Spectrophotometric methods were used to determine salivary TAC and TOS.

Results: Salivary TAC, TOS, and visfatin levels were statistically higher in patients with dental caries compared to caries-free group (p=0.035; p=0.003; p<0.001 respectively). There was a positive correlation between caries number and salivary TOS and visfatin levels.

Conclusions: Findings of this prospective study demonstrated that oxidative stress may be involved in the pathogenesis of dental caries. Salivary visfatin, TAC, and TOS may be novel markers to evaluate dental caries.

Keywords: dental caries; oxidative damage; oxidative stress; saliva; visfatin.

Introduction

Dental caries is one of the most common chronic diseases in the world. It is an infectious disease [1] with multifactorial etiology resulting from the disruption of the dynamic balance between pathological factors and protective factors [2]. This disease is a high burden on individuals, and it also causes serious expenses in health systems [3].

Saliva is the exocrine secretion of the major and minor salivary glands. Saliva, recently used in the diagnosis of many diseases, can be an alternative to time-consuming and invasive diagnostic procedures, as it is always readily available, easily and cost-free collected without the need for an invasive procedure [4]. Although 99% of its content is water, it consists of various organic and inorganic substances such as proteins, immunoglobulins, electrolytes, minerals, enzymes, and cytokines. The proportions of saliva components are important for the function of protection and maintaining the health of the oral cavity [5]. It is known that many components of saliva have been associated with caries risk [6].

Visfatin is a 52 kDa adipokine, discovered by Fukuwara in 2005, that has been shown to lower plasma glucose levels by binding insulin receptors in mice [7]. However, the same molecule was previously discovered and named as Pre-B Colony Enhancing Factor, involved in the early development of B-cell growth factor and cytokine-like effects. Visfatin is also known as nicotinamide phosphoribosyl transferase (NAMPT) which is the rate-limiting step in the biosynthesis of nicotinamide adenine dinucleotide
Visfatin is synthesized from lymphocytes, activated macrophages, neutrophils, hepatocytes, and pneumocytes [8]. It is found in many biological fluids including blood, saliva, and gingival crevicular fluid and is considered as an inflammatory cytokine.

Oxidative stress is a pathological condition that occurs as a result of impaired balance of the oxidative system in favor of oxidants through excessive free radical production or decreased antioxidant system function. In recent years, it has been revealed that many diseases are associated with increased free radical activity, and the active role of oxidative stress in the pathogenesis of diseases has been pointed out. Since measuring different antioxidant or oxidant molecules separately is impractical, requires complicated techniques and their effects would probably be additive, the total antioxidant capacity (TAC) and oxidant capacity of a sample is measured and defined as TAC and total oxidant status (TOS), respectively. Reactive oxygen species (ROS) are released in metabolic and physiological processes in the human body, and they are removed through enzymatic and non-enzymatic antioxidative mechanisms.

Dental plaque consists of a large number of bacteria that adhere to the tooth surface. These bacteria metabolize carbohydrates to provide energy and produce organic acids as a byproduct, which induces demineralization of tooth enamel and ultimately causes tooth decay. Cariogenic bacteria also enhance the release of many virulence factors, which is the main determinant of cariogenic plaque [9]. NADH oxidase in Streptococcus mutans, a major pathogen of dental caries, is an essential enzyme for the regeneration of NAD$^+$ during glycolysis as well as the reduction of diatomic oxygen in order to prevent ROS formation [10]. Moreover, in response to the colonization of microorganisms, the host immune system can induce the secretion of salivary antioxidants and many cytokines as a result of tissue defense mechanism [11]. Free radicals and ROS in the mouth also originate from polymorphonuclear neutrophils, primarily to inhibit bacterial growth [12].

The oxidant and antioxidant systems have been confirmed as one of the important contributory etiologic factors in many oral conditions including dental caries and it has been argued that saliva may be the first line of defense against free radical-mediated oxidative stress [13, 14]. Saliva plays an important role in caries development and its composition can be changed by any physiological and pathological conditions including dental caries. There are many studies investigating the relationship between salivary visfatin levels and periodontitis and gingivitis in recent years, and most of these studies showed increased visfatin levels [15, 16]. No study has been conducted yet with regard to salivary visfatin evaluation in patients with dental caries. Visfatin has also been shown to increase ROS derivatives [17]. Although several studies have shown that salivary TAC is elevated in early childhood caries [12, 13], the role of antioxidants and antioxidant-related mechanisms is not fully understood. There is a lacuna of studies examining the relationship between salivary TAC and TOS levels with dental caries, particularly in adults. Therefore, in this present study, our aim was to evaluate the levels and role of salivary visfatin, TAC, and TOS in dental caries to determine the role of oxidative stress in the pathogenesis of dental caries and tissue destruction.

## Materials and methods

### Study population

A total of 165 individuals aged 18–54 years, who were admitted to Selcuk University Department of Restorative Dentistry, were included in the study. Saliva samples were collected from 50 healthy individuals and 133 patients with dental caries, 18 patients were excluded from the study due to incomplete clinical data (the remaining 115 patients with dental caries, 50 caries-free controls). General exclusion criteria included chronic systemic disease, active systemic inflammatory disease, use of the drug, BMI $\geq 30$ and pregnant women. Local exclusion criteria included oral tumor, aggressive periodontitis, oral infection, and salivary gland dysfunction. The participants met the following inclusion criteria: they should be over 18 years old, have good general health status, have caries-free teeth for the control group, and have at least one dental caries for the experimental group.

### Clinical examination

Clinical assessment procedures included teeth examination, oral- periodontal evaluation of mucosal status, and collection of saliva samples. Clinical and radiographic examinations were carried out to determine the number of carious teeth of the patients. Before the examination phase, the occlusal surfaces of the teeth were cleaned carefully with soft brushes and then dried. Intra-oral examinations were performed using a dental mirror and ball-ended dental probe by a single examiner. Clinically visible large carious surfaces are detected, and diagnoses are supported with panoramic and bitewing radiographs. Decayed, Missing, and Filled Teeth (DMFT) score was calculated for each patient.

### Saliva collection

A standard stimulated saliva collection method is used. Saliva samples from the subjects were collected between 09:00 and 11:00 a.m. in order to prevent diurnal variation. All participants were asked to abstain from eating and drinking for at least 2 h. Individuals were seated comfortably in an upright position, rinsed their mouths with water before collecting saliva, and then waited 10 min prior to
collection. Participants chewed 0.5 g of paraffin for 30 s, the accumulated saliva was spit into a disposable sterile laboratory container with a wide opening and saliva collection was performed for 90 more seconds with continuous spitting. After, whole stimulated saliva samples were transferred into Eppendorf microtubes, and then samples were centrifuged at 10,000×g for 5 min to remove tissue debris. Saliva supernatants were stored at −80°C until the analysis time. The informed consent form was signed by all patients prior to saliva collection. The study was approved by Selcuk University Defense Research Ethics Committee (2017/172).

**Visfatin analysis**

Salivary visfatin levels were determined using the enzyme-linked immunosorbent assay (ELISA) method by Human Visfatin C-terminus ELISA kit (Phoenix Pharmaceuticals Inc., CA, USA) (Cat. No: EK-003-80). The analytic sensitivity for visfatin was 2.3 ng/mL, intra-assay coefficient variation (CV) was <10%, and inter-assay CV was <15%.

**TAC–TOS analysis**

Salivary TAC and TOS were determined using an automated measurement method (Bel Assay Diagnostics kit, Mega Tip, Gaziantep, Turkey), by Erel’s colorimetric method [18, 19]. Briefly, TOS was measured by oxidizing ferrous ions (Fe²⁺) to ferric ions (Fe³⁺) in the presence of varied oxidative species in an acidic environment. Xylenol orange was used as an indicator and results were expressed in μmol/L H₂O₂ equivalent (μmol/L H₂O₂). TAC measurement was relied on the change in the absorbance at 660 nm due to the reduction of ABTS+ to ABTS [2,2-azino-bis-(3-ethyl-benzothiazoline-6-sulphonate)] and results were expressed in mmol/L Trolox. Oxidative stress index (OSI) was counted according to TOS/TAC formula. For TAC measurement, inter-assay CV was 2.8% and the intra-assay CV was 3.3%. For TOS measurement, inter-assay CV was 3.2% and the intra-assay CV was 3.9%.

**Statistical analysis**

Data analysis was performed using SPSS version 15 (SPSS Inc, Chicago, IL, USA). Kolmogorov–Smirnov analysis was used to test for Gaussian or non-Gaussian distribution. For Gaussian-distributed data, an independent samples t-test was used to assess the significance of differences between two groups. If the data does not have a normal distribution, the Mann–Whitney U test was performed for comparisons between groups. The correlations were assessed using Spearman’s rank test for non-Gaussian-distributed variables. Based on power analysis for the sample size, the power was calculated as 99.8%. A p-value ≤ 0.05 was considered statistically significant.

**Results**

A total of 50 caries-free individuals (23 males, 27 females) with a mean age of 28.1 ± 6.2 years, 115 patients (52 males, 63 females) with dental caries had a mean age of 32.8 ± 8.3 years were included in this study. No statistical differences were found between groups in regard to age and sex (p > 0.05).

Visfatin, TAC, and TOS were detectable in all samples. The median salivary TAC, TOS, and visfatin values were significantly higher in the experimental group than in the caries-free group (p=0.035, p=0.003, p<0.001 respectively). The descriptive statistics (median and percentage values) and their comparisons are provided in Table 1.

Spearman’s correlation analysis showed a positive correlation between salivary visfatin levels with TOS and OSI. Similarly, TOS had a positive correlation with visfatin, OSI, and TAC. There was no significant correlation between salivary TAC and visfatin levels. Correlations of laboratory parameters with each other are given in Table 2.

In terms of clinical parameters, there was a positive correlation between DMFT index, caries number, and salivary visfatin levels. Salivary TOS and OSI were also positively correlated with DMFT index and caries number. On the other

### Table 1: Comparison of laboratory parameters in caries active group and caries-free group.

| Parameters | Healthy Median (25–75%) | Patients with dental caries Median (25–75%) | p-Value |
|------------|-------------------------|------------------------------------------|---------|
| Visfatin, ng/mL | 66.58 (40.4–88.9) | 136.12 (80.4–204.3) | <0.001 |
| TAC, mmol Trolox Eq/L | 0.42 (0.32–0.6) | 0.51 (0.43–0.67) | 0.035 |
| TOS, μmol H₂O₂/L | 0.74 (0.52–2.8) | 2.6 (0.98–11.79) | 0.003 |
| OSI, arbitrary units | 1.69 (0.58–9.35) | 5.42 (1.37–20.96) | 0.008 |

TAC, total antioxidant capacity; TOS, total oxidant status; OSI, oxidative stress index.

### Table 2: The correlations of the laboratory parameters (visfatin, TAC, TOS, and OSI) with each other.

| Spearman’s Rho | TAC | TOS | OSI | Visfatin |
|----------------|-----|-----|-----|---------|
| TAC r           | 1   | 0.412 | 0.202 | 0.092 |
| p               |     | <0.001 | 0.009 | 0.238 |
| TOS r           | 1   | 0.968 | 0.244 |        |
| p               |     | <0.001 | 0.002 |        |
| OSI r           | 1   | 0.256 | 0.001 |        |
| p               |     |       |       |        |
| Visfatin r      | 1   |     |       |        |
| p               |     |       |       |        |

TAC, total antioxidant capacity; TOS, total oxidant status; OSI, oxidative stress index.
Table 3: Correlation analysis of laboratory parameters (visfatin, TAC, TOS, and OSI) and clinical parameters (DMFT index and caries number).

|                  | Spearman’s Rho | TAC | TOS | OSI | Visfatin |
|------------------|----------------|-----|-----|-----|----------|
| Caries number    | r              | 0.052 | 0.283 | 0.314 | 0.502 |
|                  | p              | 0.582 | 0.002 | 0.001 | <0.001 |
| DMFT index       | r              | 0.120 | 0.245 | 0.240 | 0.326 |
|                  | p              | 0.153 | 0.003 | 0.004 | <0.001 |

DMFT, Decayed, Missing, and Filled Teeth; TAC, total antioxidant capacity; TOS, total oxidant status; OSI, oxidative stress index.

Table 4: The diagnostic value of laboratory parameters and ROC analysis.

|                  | AUC | SE  | 95% CI        |
|------------------|-----|-----|---------------|
| Visfatin         | 0.771 | 0.037 | 0.699–0.844 |
| TAC              | 0.604 | 0.049 | 0.508–0.700 |
| TOS              | 0.643 | 0.048 | 0.550–0.737 |

TAC, total antioxidant capacity; TOS, total oxidant status; AUC, area under the curve; SE, standart error; CI, confidence interval.

hand, TAC had no correlation with the DMFT index and caries number. Correlation analysis results between laboratory tests and clinical parameters are given in Table 3.

Based on the Receiver operating characteristic curve (ROC) analysis, which was carried out to determine the diagnostic value of visfatin, TAC and TOS in detecting dental caries, the area under the curve (AUC) values were 0.771, 0.604, and 0.643, respectively. ROC analysis and AUC data are shown in Table 4 and Figure 1.

Discussion

The analysis of saliva biomarkers is accepted as an alternative to serum and plasma by many authorities [20]. Since saliva is easy and non-invasive to collect, contains many biomarkers in its composition, and is affected by both intraoral and systemic events, it is a valuable diagnostic and research tool. In case of dental caries, some alterations in its composition may occur, increasing its diagnostic value.

Oxidative stress can be defined as the impaired balance between the production of free radicals and the antioxidant defense mechanism of the organism, which directly or indirectly results in cell damage. Oxidative stress can be responsible, with varying degrees of importance, for the pathogenesis of many diseases such as diabetes, atherosclerosis, hypertension, obesity, cancer, and inflammation [21]. Recently, attention has focused on the role of oxidative stress in the onset and/or progression of dental diseases including dental caries, which is a common and preventable chronic disease. According to the results of this present study, salivary TAC and TOS were found to be higher in the dental caries group compared to healthy subjects, thus also confirming the hypothesis established by this study. TAC is the amount of free radical scavenged by a test solution used to determine the antioxidant capacity of biological samples [22]. The general belief is that salivary TAC levels are increased in dental caries, although there are few studies to suggest otherwise [23, 24]. Ahmadi-Motamayel et al. indicated that salivary TAC was higher in individuals with dental caries compared to the control...
Hataysal et al.: Relationship between dental caries and saliva’s visfatin levels, TAS, and TOS

antioxidants, non-enzymatic endogenous antioxidants, exogenous antioxidants, and dental caries, which are evaluated separately, may contribute to the understanding of the dental caries mechanism. At rest, the submandibular salivary gland secretes 65% of all saliva. However, parotid salivary gland secretion is more dominant in stimulated saliva and the parotid salivary gland is the main source of antioxidants and proteins [25]. Since total protein, nitrite, TAC and TOS concentrations increased in stimulated saliva [4, 33], stimulated saliva was preferred in our study.

Visfatin acts as an inflammatory cytokine by increasing leukocytes activation, adhesion molecules’ synthesis, proangiogenic activity and production of proinflammatory and inflammatory cytokines [34]. Furthermore, it provides macrophages to survive longer and inhibit neutrophil apoptosis, prolonging the duration of neutrophils and leading to tissue destruction [35]. Recent studies demonstrated a complex and close interaction between visfatin and oxidative stress and concluded that visfatin can induce oxidative stress, as well as in the modulation of some miRNA and target genes [17, 36]. Büyükyaydın et al. showed a positive correlation between circulating visfatin levels and TOS [37]. In this present study, salivary visfatin levels were evaluated and salivary visfatin levels were found to be higher in patients with dental caries than those of healthy subjects. Visfatin concentrations were also positively correlated with caries number. According to our hypothesis, increased visfatin levels may mediate tissue damage in the formation or pathogenesis of dental caries as well as disruption in the integrity of dental tissue. Mamali et al. reported that contrary to resistin and adiponectin, there was no correlation between salivary visfatin levels and serum visfatin levels [20]. The reason of these differences may be that, in response to intraoral changes, salivary glands also secrete many proteins including visfatin which can take part in the pathogenesis of caries by locally affecting dental tissues that may result in the destruction of dental structures. There are several that demonstrated a significant increase in salivary visfatin levels in periodontitis and gingivitis [15, 16]. Ozcan et al. reported that salivary visfatin levels are higher particularly in the gingivitis group (n:24) and in the periodontitis group (n:25) than in the healthy group (n:23) [16]. However, salivary visfatin measurement was inadequate in the differentiation of gingivitis and periodontitis. Tabari et al. reported that salivary visfatin levels were higher in subjects with periodontitis (n:20) than in healthy subjects (n:20) [15]. On the contrary to these researches, Kadkhodaizadeh et al. found no association between periodontitis and salivary visfatin levels [38]. Therefore, gingivitis and periodontitis may also have an effect on salivary visfatin levels.

To the author’s knowledge, this present study is the first study to investigate the relationship between salivary
visfatin concentrations and dental caries. The number of samples in our study is considerably higher than in previous studies. In addition, our results show a positive correlation between visfatin concentrations and caries number. Therefore, salivary visfatin concentration can be used as a marker to assess the potential caries risk of individuals. In the future, both visfatin and oxidative stress in saliva could be used for screening purposes by evaluating the risk of dental caries in large populations. Moreover, a better understanding of the role of oxidative stress in dental caries can provide new treatment strategies using host modulation techniques.

The limitations of this study are the difficulties of constructing a control group without periodontal tissue diseases and dental caries, and an experimental group with only dental caries without periodontal tissue diseases. In view of the above studies, more comprehensive studies with larger groups with both dental caries and periodontal diseases are needed.

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