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Evaluation of the Serum Levels of Osteopontin in Iranian Patients with Benign and Malignant Salivary Gland Tumors

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Abstract

Background: Osteopontin (OPN) is involved in various biological functions, including cancer pathogenesis and metastasis. However, its clinical value in salivary gland tumors (SGTs) has received little attention. Therefore, this study aimed to evaluate the connection between OPN serum levels and the clinicopathologic features of benign and malignant SGTs in Iranian patients.

Methods: This cross-sectional study involved a total of 90 patients with SGTs, including malignant ($n=60$) and benign ($n=30$) cases. The control group consisted of 60 healthy individuals matched by age and sex to the patient group. An enzyme-linked immunosorbent assay (ELISA) kit was employed to quantify OPN serum levels in samples.

Results: OPN serum levels were significantly elevated in patients compared to the control group (23.16±11.08 ng/mL *vs*. 10.61±4.99 ng/mL, $P<0.0001$). There were also significant differences in OPN serum levels between malignant and benign cases of SGT (26.64±11.73 ng/mL *vs*. 16.19±4.68 ng/mL, $P<0.0001$). Additionally, OPN concentration was significantly associated with the clinicopathologic characteristics of patients, including tumor size, tumor node metastasis (TNM) classification, and lymph node involvement, but not with patients' gender, age, and the size and type of lesions.

Conclusion: Based on the findings, OPN serum levels could be used as a supportive biomarker to diagnose SGTs and differentiate between benign and malignant cases. This is a preliminary study; therefore, additional research with a larger number of participants and extended monitoring periods is necessary to evaluate the potential of OPN in more effectively diagnosing SGTs in their early stages.

Keywords: Osteopontin, Salivary gland tumors, Clinicopathologic characteristics

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Introduction

Salivary gland tumors (SGTs) represent up to 6% of all head and neck neoplasms and are infrequently observed in the field of oral pathology (1). These tumors have diverse origins and pathologies, existing in both benign and malignant forms (2). They are generally classified based on their location, either within the major salivary glands, which include the parotid, submandibular, and sublingual glands, or within the minor salivary glands. SGTs are clinically characterized by a mass in the head and neck region and pulsing pain that worsens over time (3-5). Although the oral cavity is readily accessible, early identification of SGTs can be challenging, leading to many patients being diagnosed at advanced stages of the disease. Diagnosing tumors at earlier stages is important for successful treatment and might lessen the impact on a patient's life. However, the diagnosis and management of SGTs pose challenges for both patients and clinicians due to their rarity, complex clinical and pathological characteristics, overlapping morphological features among different entities, and the prolonged risk of recurrence (1, 6, 7).

Osteopontin (OPN) is a glycophosphoprotein with a wide range of physiological and pathophysiological functions (8). It exists in various forms, facilitates cell-matrix interactions, and mediates adhesion, migration,

and survival in many types of cells. OPN is expressed in osteoclasts, osteoblasts, nerve cells, endothelial cells, fibroblasts, and epithelial cells of various organs. It is also secreted in bodily fluids such as blood, milk, and urine (8,9). At sites of inflammation, OPN is secreted from various immune cells, including activated T lymphocytes, macrophages, and leukocytes, and is involved in the pathogenesis of autoimmune and chronic inflammatory disorders (10-12). Splicing variants of OPN also play a role as tumor promoters and are involved in every step of tumor aggressiveness, including cell proliferation, angiogenesis, and the development of distant metastases. However, the mechanisms by which OPN promotes malignant behavior are still unclear (13). Signaling proteins such as growth factors and oncogenes are correlated with the overexpression of OPN in tumors; hence, researchers have focused on OPN suppression as a promising strategy for cancer therapy (13-15). Accumulating evidence to date has indicated that increased levels of OPN contribute to the progression of human cancers such as melanoma (16–18), glioblastoma (19,20), laryngeal and hypopharyngeal carcinoma, as well as skin, brain, lung, kidney, liver, bladder, breast, pancreatic, gastric, colorectal, prostate, and ovarian cancers (9,13,21). The clinical significance of OPN in SGTs is still poorly understood. Therefore, this study investigated the serum levels of OPN in Iranian patients diagnosed with benign or malignant SGTs. Additionally, the prognostic significance of clinicopathologic features of patients was evaluated regarding OPN status.

Methods

Patients

This cross-sectional study involved 90 SGT patients who visited the ear, nose, and throat (ENT) Department of Khalili Hospital, affiliated with Shiraz University of Medical Sciences, Shiraz, Iran. The inclusion criteria required pathologically confirmed cases of benign (n = 30) or malignant (n = 60) SGTs without treatment before collecting blood samples. We excluded those with neoplasms in organs other than the salivary glands and those with a history of autoimmune, inflammatory, or systemic diseases. Medical records and demographic data were obtained from the patient database. The tumor node metastasis (TNM) stages were determined using an international staging system for SGTs, which is available at www.cancer.org. The control group for this study consisted of 60 healthy individuals matched by age and sex to the patient group. They had no history of SGTs or other types of cancer or systemic, inflammatory, or autoimmune diseases.

Evaluation of the OPN Levels

Five milliliters of whole blood was gathered in non-heparinized tubes and left to clot for half an hour at room temperature. Serum samples were then extracted by a 5-minute centrifugation at 3000 RPM and stored at -70 °C until further use.

The ELISA technique measured OPN serum levels in patient and control groups with a commercially available Human Osteopontin Quantikine ELISA Kit (R&D Systems, USA). All experiments were conducted following the manufacturer's recommendations. The serum samples were diluted 25-fold using the calibrator diluent to ensure values were within the assay's dynamic range. Human OPN standards were reconstituted with deionized water. Subsequently, 50 µL of standard, control, or sample was added to appropriate wells in a 96-well plate, which was then sealed and incubated at room temperature for 2 hours. After four washing steps, a specific polyclonal antibody for human OPN conjugated to horseradish peroxidase was added to every well, and the plate was incubated once more. Following another washing step, substrate solution was added to each microplate well. The plates were left to sit at room temperature for half an hour without any exposure to light. The enzymatic reaction was terminated by adding 2N sulfuric acid. The microplate reader (Epoch Microplate Spectrophotometer, BioTek, USA) was used to measure the optical density of each well at 450 nm with the correction wavelength set at 570 nm.

Statistical Analysis

The Statistical Package for the Social Sciences (IBM SPSS, version 21) was used for all statistical analyses. Using the Kolmogorov-Smirnov test, the variables were evaluated for normal distribution. Frequencies and percentages were used to express categorical variables. The distribution of categorical variables across the study groups was compared using Pearson's χ^2 test. Quantitative variables were reported as means and standard deviations (SD). One-way analysis of variance (ANOVA) accompanied by a post-hoc Tukey test and independent Student's *t* test were utilized to assess the differences among the groups. The relationship between OPN concentration and continuous variables was examined using Pearson's correlation coefficient. The diagnostic value of OPN for patients with SGTs was ascertained using the receiver operating characteristics (ROC) curve. A *P*-value was considered statistically significant if it was below 0.05.

Results

Overall, a total of 90 cases of pathologically confirmed SGTs and 60 healthy individuals were incorporated into the analysis. The patient group consisted of 43 males (47.8%) and 47 females (52.2%) with a mean age of 48.2 ± 17.1 years. The control group consisted of 29 males (48.3%) and 31 females (51.7%), with a mean age of 46.7 ± 14.1 years. No significant differences were observed between the patient and control groups regarding gender distributions ($P = 0.947$) and age ($P = 0.517$). The patient group was subsequently categorized into benign cases

($n=30$) and malignant cases ($n=60$). The clinical and demographic features of patients are outlined in Table 1. The serum levels of OPN in patients with SGTs were markedly elevated compared to those in the control group (23.16 ± 11.08 ng/mL *vs.* 10.61 ± 4.99 ng/mL, $P<0.0001$). The concentration of OPN was also elevated in patients with malignant SGTs compared to benign cases (26.64 ± 11.73 ng/mL *vs.* 16.19 ± 4.68 ng/mL, $P<0.0001$). Statistically significant differences were also found in the serum levels of OPN when comparing benign or malignant cases of SGT with those of healthy individuals ($P<0.0001$ and $P=0.009$, respectively). Figure 1 displays the ROC curve for serum OPN levels to distinguish between healthy individuals and patients with SGTs, as well as malignant and benign SGTs.

Correlations between the concentration of OPN and clinicopathologic characteristics of patients with SGTs were also assessed. The majority of SGTs were located in parotid glands (77.8%), followed by submandibular (16.7%) and sublingual glands (5.5%). The OPN concentrations in parotid, submandibular, and sublingual glands were 21.55 ± 10.35 ng/mL, 27.88 ± 10.95 ng/mL, and 31.48 ± 15.81 ng/mL, respectively. However, serum levels of OPN were similar among these groups ($P>0.05$). Additionally, the mean serum OPN levels were 13.21 ± 3.52 ng/mL in patients with acinic cell adenocarcinoma (ACA), 28.05 ± 7.68 ng/mL in adenoid cystic carcinoma (ACC), 28.63 ± 11.55 ng/mL in mucoepidermoid carcinoma (MEC), 14.70 ± 8.92 ng/mL in squamous cell carcinoma (SCC), 16.30 ± 4.19 ng/mL in pleomorphic adenoma (PA),

Table 1. Clinical and demographic characteristics of patients with salivary gland tumors

Parameters			Patients		
			Benign ($n=30$)	Malignant ($n=60$)	Total ($n=90$)
Sex, male (%)			12 (40.0%)	31 (51.7%)	43 (47.8%)
Age, mean ± SD			44.2 ± 13.8	50.2 ± 18.3	48.2 ± 17.1
Tumor characteristics	Location	Parotid glands	27 (90.0%)	43 (71.7%)	70 (77.8%)
		Submandibular glands	3 (10.0%)	12 (20.0%)	15 (16.7%)
		Sublingual glands	*N/F	5 (8.3%)	5 (5.6%)
	Type	Acinic cell adenocarcinoma	N/F	4 (6.7%)	4 (4.4%)
		Adenoid cystic carcinoma	N/F	14 (23.3%)	14 (15.6%)
		Mucoepidermoid carcinoma	N/F	27 (45.0%)	27 (30%)
		Squamous cell carcinoma	N/F	4 (6.7%)	4 (4.4%)
		Pleomorphic adenoma	25 (83.3%)	N/F	25 (27.8%)
		Others	5 (16.7%)	11 (18.3%)	16 (17.8%)
	Size	Main tumor, mean ± SD	3.8 ± 1.8	3.7 ± 1.9	3.79 ± 1.86
		≤4 mm, *n* (%)	17 (56.7%)	40 (66.7%)	57 (63.3%)
		>4 mm, *n* (%)	13 (43.3%)	20 (33.3%)	33 (36.7%)
	Lymph node involvement, *n* (%)		N/F	21 (35.0%)	21 (23.3%)

N/F: not found.

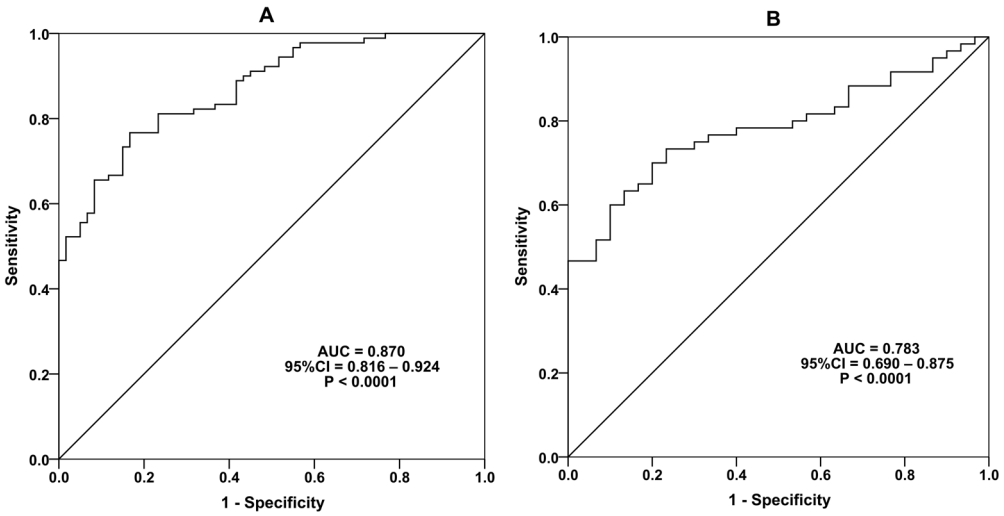

Figure 1. ROC curve analysis for serum OPN levels to distinguish between patients with SGTs and healthy controls (A), as well as between malignant and benign SGTs (B)

and 24.95 ± 14.02 ng/mL in other tumor types. Figure 2 displays serum OPN concentrations among different tumor types.

Applying a correlation coefficient test showed a significant positive correlation between the concentration of OPN and the dimensions of the primary tumor ($r = 0.287$, $P = 0.006$). However, no correlation was found between OPN concentration and the patient's age ($r = 0.073$, $P = 0.374$). According to the TNM classification, the distribution of patients with malignant SGTs diagnosed at various stages was as follows: 7 patients (11.6%) at stage I, 16 patients (26.7%) at stage II, 21 patients (35.0%) at stage III, and 16 patients (26.7%) at stage IV. Serum levels of OPN could differentiate malignant cases of SGTs at TNM stages III and IV from benign patients ($P < 0.05$), as well as TNM stages II, III, and IV from healthy controls ($P < 0.05$), as shown in Figure 3. Additionally, serum levels of OPN were markedly increased in patients exhibiting lymph node involvement ($P < 0.0001$). The serum levels of OPN were similar between males and females in the patient (22.83 ± 10.71 ng/mL *vs.* 23.46 ± 11.52 ng/mL, $P = 0.791$) and the control (11.68 ± 4.52 ng/mL *vs.* 9.61 ± 5.27 ng/mL, $p = 0.110$) groups.

Discussion

Histopathological examination of tissues has long been considered the gold standard for diagnosing and classifying human tumors. In recent decades, tissue-based biomarker tests have also been extensively used; however, they are invasive methods that carry some risk for patients. Consequently, researchers have concentrated on non-invasive methods like blood-based biomarkers for early detection of neoplasms at different stages, which may be more sensitive than histological techniques (22,23). The epithelium of secretory tissues, including the salivary glands, has been shown to express OPN, and its overexpression contributes to the tumorigenicity and metastasis of cancer cells via several different pathways (15,24). Despite a wide range of OPN expression in several types of human tumors, limited data regarding benign or malignant SGTs have been found in the literature. To our knowledge, OPN expression has been immunohistochemically verified in both normal salivary gland tissue and certain SGT types (24-29). However, the present study is the first report investigating OPN serum levels in Iranian patients with SGTs.

Based on the findings, we detected OPN in the serum of all study participants using an ELISA assay. The OPN levels in the serum of SGT patients were significantly higher than those of the healthy controls. Previous studies that immunohistochemically assessed OPN expression in SGTs have reported contradictory results. Coppola et al (27) found no OPN expression in most SGTs (10 out of 14, 71.4%); however, they observed a significant correlation between the OPN expression score and tumor stage. In another study, OPN was expressed in all surgical specimens from 175 patients with primary SGTs, with ACC having the highest mean score compared to MEC and ACA (28). Fok et al (29) used immunohistochemistry to semi-quantify the levels of OPN expression in normal salivary gland tissue ($n = 20$), PA ($n = 20$), ACA ($n = 11$), and MEC ($n = 29$). Their results showed a significant increase in the expression of OPN in ACA and MEC samples compared to PA and normal salivary glands. Darling et al (24) also examined OPN expression in normal salivary gland tissue ($n = 23$) and three types of SGTs, including PA ($n = 11$), ACC ($n = 14$), and polymorphous low-grade adenocarcinoma (PLGA) ($n = 12$). They found OPN expression in all samples, but normal salivary gland tissues had lower levels of OPN expression than PA and PLGA. In contrast, the difference between ACC and normal salivary gland tissues was insignificant. This is surprising, as ACC is known to have the most malignant potential; hence, it

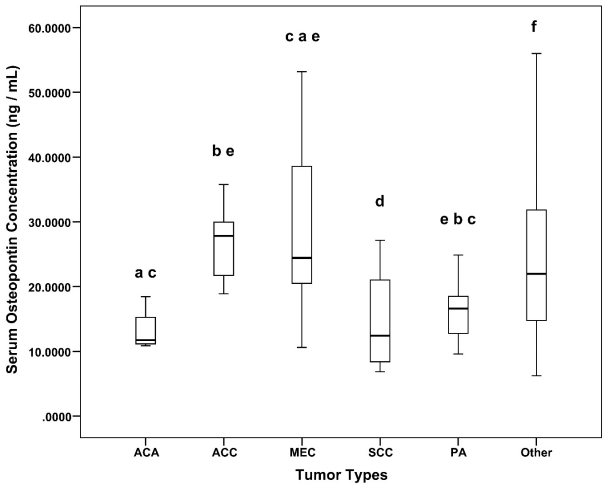

Figure 2. Serum OPN concentrations among different tumor types. The same small letter on the boxes showed statistically significant differences among the tumor types ($P < 0.05$)

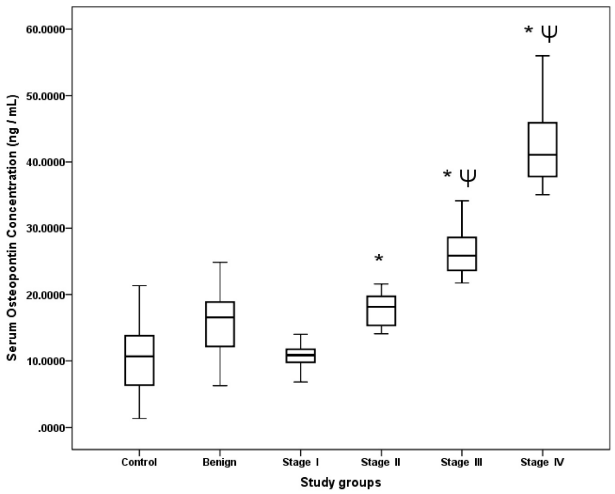

Figure 3. Serum levels of OPN in the control group, benign cases, and malignant cases at different TNM stages. Asterisk (*) and Psi (Ψ) indicate statistically significant differences in malignant cases ($P < 0.05$) in comparison to control and benign groups, respectively

should have more expressed OPN than normal tissue. In contrast to Darling et al (24), we detected higher levels of OPN in patients with ACC than in healthy controls.

The current investigation has also revealed higher levels of OPN in the serum of patients with malignant SGTs compared to benign cases, indicating that OPN is a marker for tumors that exhibit more aggressive characteristics. Consistent with our results, some studies have found that OPN is significantly more expressed in malignant tumors than in benign lesions (14,30). Due to the complex histopathological characteristics and varied clinical behaviors, diagnosing benign and malignant SGTs poses numerous challenges (1,6). Therefore, a significant difference in OPN serum levels between our benign and malignant cases of SGTs not only suggests its clinical significance but also confirms its association with tumorigenesis and metastasis.

The capacity of cancer cells to generate and release OPN, passive discharge from necrotic cells, and active secretion by inflammatory or immune cells can all be associated with the levels of OPN present in serum. However, with the current tools, determining the exact source of OPN in patients' serum is impossible. Elevated levels of OPN can lead to changes in the expression of other genes involved in the progression of neoplasms (9-12). It is important to note that OPN isoforms have distinct expression profiles and biological effects, which may partly explain the diverse expression patterns observed in various types of SGTs, even within a particular cancer type. Additionally, varying degrees of post-translational modifications of OPN, such as glycosylation, phosphorylation, sulphation, etc., can have functional effects and determine the cell's response to OPN, generating variants of OPN with different malignant potentials (24,28). Therefore, the different OPN ranges found in SGTs could be connected to the unique circumstances of each cancer type.

On the other hand, the expression of OPN may be influenced by various clinicopathologic characteristics of patients, including age, sex, tumor location, tumor dimensions, tumor stage, lymph node involvement, and the presence of distant metastasis (24,27). Serum OPN levels in our study were substantially correlated with lymph node involvement, advanced TNM stage, and larger tumor size. Compared with the healthy controls and benign cases, patients at the advanced stage of SGTs exhibited increased levels of OPN; however, those at stage I had no significant difference. This could be attributed to the limited number of patients in stage I (7 cases) in comparison to healthy ($n=60$) or benign ($n=30$) subjects. Consequently, the scope of our analysis was restricted, and additional research is required to confirm this finding. Previous studies have suggested that overexpression of OPN may be a marker of high-stage cancers as it is preferentially expressed by tumor cells with invasive and metastatic properties, which is compatible with our findings (31-35). However, the correlation of OPN expression with clinicopathologic characteristics of patients was insignificant in some papers (28,36).

This research is subject to significant limitations arising from methodological flaws, such as the lack of prior sample size estimation. In addition, a limited number of patients with SGTs were assigned to multiple unequal subgroups; however, we included as many cases per group as possible. Although the analyses revealed significant differences among the study groups in several parameters, the patient population was not assessed to determine whether OPN serum levels could be a prognostic predictor for long-term survival.

Conclusions

The increase in OPN serum levels in patients with SGTs compared to the healthy group and its association with lymph node involvement, advanced TNM stage, and larger tumor size suggests that OPN is a supportive diagnostic biomarker. Additionally, its role in invasiveness and metastasis makes it a valuable tool for distinguishing between benign and malignant cases of SGTs. However, due to the limited number of patients and the scarcity of reports regarding the role of OPN in SGTs, it is essential to conduct further clinical studies that involve larger sample sizes and extended follow-up periods to clarify the functional role of OPN in the tumorigenicity of salivary glands.

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Authors' Contribution

Conceptualization: Azadeh Andisheh Tadbir, Bijan Khademi, and Maryam Mardani.
Data curation: Maryam Jamilzadeh and Bijan Khademi.
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Funding acquisition: Maryam Mardani.
Investigation: Azadeh Andisheh Tadbir, Maryam Jamilzadeh, and Maryam Mardani.
Methodology: Maryam Jamilzadeh and Mahyar Malekzadeh.
Project administration: Maryam Mardani.
Resources: Maryam Mardani.
Software: Javad Moayedi.
Supervision: Maryam Mardani.
Validation: Azadeh Andisheh Tadbir, Bijan Khademi, and Maryam Mardani.
Visualization: Maryam Mardani.
Writing–original draft: Javad Moayedi.

Competing Interests

The authors declare that they do not have any conflict of interest.

Ethical Approval

Written informed consent was obtained from all participants before they were enrolled in this study following the Declaration of Helsinki and its later amendments. The study protocol was approved by the

Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (approval ID: IR.SUMS.DENTAL.REC.1398.136; approval date: 2020.01.05).

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