Impaired spontaneous secretion as a potential factor in the development of sialolithiasis in the submandibular gland: A preliminary sialoscintigraphic study

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Abstract

Objectives: The development of sialolithiasis is commonly related to local factors, such as the retrograde migration of foods, bacteria, or foreign bodies from the oral cavity. The association of sialolithiasis and saliva stasis resulting from decreased spontaneous secretion remains largely unexplored. The current study investigated the potential role of impaired spontaneous secretion in association with the formation of submandibular gland calculi.

Study Design: A retrospective cohort study.

Methods: Between September 2016 and December 2017, 11 patients with unilateral submandibular gland sialolithiasis confirmed with sialendoscopy were assigned to the experimental group. Another 35 patients clinically diagnosed with parotid obstructive sialadenitis were assigned as the control group. The slope changes of the isotope count curve of the unaffected submandibular gland in the experimental group and the bilateral submandibular glands in the control group were calculated and compared to estimate the spontaneous secretion differences. The degree of spontaneous secretion was defined as the slope changes in the steady ascending stage of the scintigraphic exam.

Results: The slope decline (degree of spontaneous secretion) on the unaffected side in patients with single-gland submandibular obstructive sialadenitis was significantly lower than that in the control individuals (p = .002). In contrast, the between-group comparison in the unaffected parotid glands revealed no difference in the slope decline.

Conclusion: The spontaneous secretion of the submandibular gland in patients with submandibular sialolithiasis was decreased compared to that in patients without submandibular sialolithiasis. This phenomenon might be associated with the development of sialolithiasis.

Level of Evidence: 3.

Keywords
salivary scintigraphy, sialolithiasis, spontaneous secretion, submandibular gland

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1 | INTRODUCTION

Sialolithiasis represents approximately 66% of the cause of obstructive sialadenitis, and approximately 83% of sialoliths originate within the submandibular glands. Under normal circumstances, salivary secretion is provoked by masticatory/gustatory stimuli and higher brain structure stimuli. The greater incidence of submandibular gland stones was due to the higher alkaline and mucous content of secretions and longer excretory ducts with antigravity flow than those of parotid glands. Interestingly, unlike bile stasis, which is known to be associated with the development of gallstones, no study has attempted to reveal the possible relationship between the development of sialolithiasis and decreased salivary gland secretion. Salivary gland secretion plays an essential role in supporting upper gastrointestinal tract function and maintaining oral well-being. A little over 65% of all resting saliva is derived from the submandibular glands; in contrast, parotid glands contribute up to 50% of stimulated secretion. In other words, the principal function of the parotid glands is digestive function, whereas submandibular glands are chiefly responsible for sustained lubrication and protection. Some studies have revealed that the unstimulated salivary flow rate for submandibular glands was approximately three times higher than that for parotid glands. Spontaneous secretion in submandibular glands has been observed in salivary scintigraphy in different studies. This phenomenon indicates that the secretion of submandibular glands influences oral wetness during the day without the stimulation of oral intake. So far, several mechanisms associated with the development of sialolithiasis have been studied. John D. Harrison proposed that the initial sialomicrolith formation followed by an inflammatory reaction and subsequent glandular fibrosis and atrophy may lead to decreased secretion and possible retrograde microbial invasion with ensuing sialolith. Schapher et al. studied the components of salivary stones and revealed that neutrophil extracellular traps (NETs) might play a pivotal role in interconnecting the above mechanisms that lead to sialolith formation. On the other hand, whether decreased spontaneous submandibular secretion constitutes one of the factors in the generation of sialolithiasis remains largely uninvestigated. By comparing the degree of submandibular gland spontaneous secretion under sialoscintigraphy, the purpose of this study was to verify the potential role of impaired spontaneous secretion in association with the formation of submandibular gland calculi.

2 | MATERIALS AND METHODS

2.1 | Study population

This retrospective study was approved by the Institutional Review Board of Taipei Medical University Hospital (TMU-JIRB N201706053). Between September 2016 and December 2017, 46 patients with clinical suspicions of obstructive sialadenitis who underwent salivary gland scintigraphic examinations were enrolled from Taipei Medical University Hospital and Mackay Memorial Hospital, Taipei, Taiwan. Eleven patients who received sialendoscopic surgery were assigned as the experimental group in whom unilateral submandibular sialolithiasis was verified. Another 35 patients clinically diagnosed with uni- or bilateral parotid obstructive sialadenitis were assigned to the control group, under the consideration that currently there is no evidence of significant compensatory over-excretion in submandibular glands in the situation of parotid dysfunction. Informed consents have been retrieved from all the above-included patients.

Patients with the following history were excluded: dry mouth, autoimmune disease, operation in salivary gland, having received external radiotherapy over the regions of head and neck, having received radioactive iodine therapy, or regular intake of medications that would influence salivary flow. A simplified schematic diagram of the study is shown in Figure 1.

2.2 | Imaging acquisition and general sialoscintigraphic data analysis

Sialoscintigraphy protocols were described in our previous study. In brief, after fasting for more than 2 h before the exam, subjects received intravenous injection of 259 MBq (7 mCi) of 99mTc-pertechnetate followed with sequential image acquirement every 30 s. This phenomenon indicates that the secretion of submandibular glands influences oral wetness during the day without the stimulation of oral intake.

As shown in Figure 2B, with equal-sized regions of interest, a schematic presentation of the time-activity curves of the four salivary glands was generated (Figure 2C). Five semi-quantitative parameters were calculated as followed: (1) the uptake ratio (UR) was the quotient calculated from the result for peak activity of the salivary gland divided from the background activity. (2) Two parameters as maximum accumulation (MA), and maximum excretion (ME), were calculated using the equation (b – a)/b (%), and (b – c)/b (%), respectively. As shown in Figure 2C, “a” is the activity in the first minute (assumed to be vascular perfusion activity); “b” represents the peak activity, and “c” denotes the value of the lowest activity after acid stimulation. (3) Another two parameters as T_max, which indicates the time required for the corresponding gland to reach maximal activity, and T_max, which was defined as the interval between the peak and the lowest activity point after acid stimulation, were also documented.

The UR and MA parameters reflect the quantity of accumulation. T_max and T_max represent the estimation of the velocity of isotope accumulation and excretion, respectively, and ME refers to the proportion excreted.

2.3 | Analysis of spontaneous submandibular gland secretion by slope comparison of the sialoscintigraphic curve at the steady ascending phase

The time-activity curves of the parotid glands tended to rise “steadily” and reach a plateau before gustatory stimulation, whereas the
Submandibular glands often showed a “downbending” pattern during the period of isotope uptake, indicating spontaneous secretion. The temporal change in the slope of the rising curve in sialoscintigraphy can be used to estimate unstimulated spontaneous secretion in submandibular glands, as the degree of downbending implies the degree of spontaneous secretion. Theoretically, if there is no spontaneous secretion, the time-activity curves ascend as a straight line during the steady ascending phase. Exact isotope count numbers of ROIs of each salivary gland at the 2nd, 4th, and 6th minute were retrieved using Siemens workstation software to compare the time-activity curve slope changes at the steady ascending phase. The slope difference of the counts of the unaffected submandibular gland in the experimental group and that of the bilateral submandibular glands in the control group were calculated using the equation $m = (b' - a')/2 - (c' - b')/2$, where $a'$, $b'$, and $c'$ represent the count numbers of the 2nd, 4th, and 6th minute of the corresponding scintigraphic time-activity curves (Figure 3).
2.4 | Statistical analysis

The demographic data are given as absolute numbers or presented as the mean (SD). Comparisons of the mean values of the five semi-quantitative parameters (UR, maximal accumulation, maximal excretion, \( T_{\text{max}} \), and \( T_{\text{min}} \)) and slope difference between the experimental group and the control group were calculated using an independent \( t \)-test. On the other hand, comparisons of the parameters mentioned above and slope difference between the bilateral parotid glands in the experimental group and values of the unaffected parotid glands in the control group were also carried out. A normality test for populations with a normal distribution was performed using the Kolmogorov–Smirnov test. The Levene test of homogeneity was also examined before conducting an independent \( t \)-test. The Mann–Whitney \( U \) test was used as a nonparametric analysis. Data were analyzed with the Statistical Package for Social Sciences (SPSS 23; IBM, Armonk, USA). In this study, a \( p \)-value of <.01 was regarded as statistically significant to reduce the bias resulting from a limited number of enrolled cases.

3 | RESULTS

3.1 | Patient demographics and general sialoscintigraphic parameter comparison

There was no significant age or sex difference between the experimental and control groups. No significant difference was found for any of the five quantitative scintigraphic indicators between the experimental and control groups (Table 1).

4 | SLOPE COMPARISON OF THE SIALOSCINTIGRAPHIC CURVE AT THE STEADY ASCENDING PHASE

By calculating the slope differences between 2–4 and 4–6 min in the steady ascending stage of the scintigraphic exam as in Figure 3, the slope decline (degree of downbending) in the experimental group (unaffected side of submandibular glands in patients with single-gland submandibular obstructive sialoadenitis) was significantly lower than that in the control group (bilateral submandibular glands in patients with uni- or bilateral parotid obstructive sialoadenitis) \( (p = .002) \) (Table 2), suggesting decreased spontaneous secretion in the experimental group patients.

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**TABLE 1** Demographic variables and comparison of scintigraphic parameters

| Patient group | Unaffected side of submandibular gland | Bilateral submandibular glands | \( p \) value |
|---------------|----------------------------------------|-------------------------------|-------------|
| **Age (years)** | 43.9 (15.0) | 47.1 (11.7) | .471 |
| **Gender (M:F)** | 7:4 | 10:25 | .085* |

| Salivary scintigraphic parameters | | |
|----------------------------------|----------------------------------|-----------------------------|
| **Uptake ratio** | 2.59 (0.71) | 2.92 (1.00) | .377* |
| **Maximum accumulation** | 47.1 (8.1) | 51.1 (12.9) | .317 |
| **Maximum excretion** | 46.2 (9.5) | 50.0 (11.8) | .301* |
| **Time at maximum count \( (T_{\text{max}}) \)** | 18.70 (0.71) | 18.23 (1.91) | .401* |
| **Total excretion time \( (T_{\text{min}}) \)** | 2.70 (1.01) | 3.16 (1.18) | .166* |

Note: Values are means (standard deviation) for the quantitative variables.

*Mann–Whitney U test is used to calculate the \( p \) value.

*Total excretion time \( (T_{\text{min}}) \) defined as time interval from stimulation to minimum count.
Nevertheless, it is commonly believed that sialolithiasis most likely results from local factors, such as hyperparathyroidism, were reported to contribute to the development of salivary gland stones. More recently, researchers have proposed a possible “retrograde theory” in the development of sialolithiasis, suggesting that a retrograde migration of foods, bacteria, or foreign bodies from the oral cavity to the duct system may lead to stone formation. In this study, we demonstrated that under sialoscintigraphic evaluations, the spontaneous secretion of the contralateral submandibular gland from patients with unilateral submandibular sialolithiasis was decreased compared to our baseline individuals who have no obstructive submandibular diseases. The findings are compatible with the previously known neuro-exocrine etiology in the development of sialolithiasis and reveal that this reduced salivary flow might occur in some individuals without the influence of surgery (parasympathectomy) or medications. To the best of our knowledge, this is the first study in which a decreased secretory function of a salivary gland by nature was proposed as a predisposing factor in the development of sialolithiasis.

Sialolithiasis is defined as a calcified stone(s) in the salivary duct and/or glands. Submandibular gland sialolithiasis is the most common (80%–90%), followed by parotid gland sialolithiasis (5%–15%). The typical clinical presentation is salivary gland swelling after eating. As the swelling persists, symptoms due to local inflammation, such as pain and trismus, emerge. In severe cases, cellulitis and even abscess formation occur, leading to salivary gland atrophy and/or fistula formation if the sialolithiasis remains untreated. Management of sialolithiasis begins with conservative measures, including medications and glandular massage for symptom relief. In some cases, intraoral sialolithotomy is performed when the stone is solitary and easily palpable through the oral cavity. The advent of sialendoscopy has made a functional change in treatment modalities. Even anatomically difficult salivary stones can probably be managed with a combined endoscopic and transcutaneous approach, leaving the choice of complete excision of the affected gland as a last resort.

Many factors have been reported to contribute to the development of sialolithiasis. Systemic factors, such as primary hyperparathyroidism, were reported to be associated with the development of salivary gland stones. Nevertheless, it is commonly believed that sialolithiasis most likely results from local factors, for instance, secondary to the stagnation of saliva in a setting of partial obstruction or inflammation of the gland. In addition, a postmortem investigation disclosed the existence of “sialomicroliths” in all normal submandibular glands and in a minority of parotid glands, in which the microcalculi may act as the nidus in the initiation of sialolith formation.

| Patient group | Uni- or bilateral parotid obstructive sialadenitis (n = 35) | p value |
|---------------|----------------------------------------------------------|---------|
| Unaffected side of submandibular gland | Bilateral submandibular glands | |
| Slope difference | 0.11 (0.31) | 0.55 (0.72) | .002* |
| Bilateral parotid glands | Unaffected side of parotid glands | |
| Slope difference | 0.24 (0.31) | 0.36 (0.51) | .352 |

Note: Values are means (standard deviation) for the quantitative variables. *Statistical significance (p < .05).

More recently, researchers have proposed a possible “retrograde theory” in the development of sialolithiasis, suggesting that a retrograde migration of foods, bacteria, or foreign bodies from the oral cavity to the duct system may lead to stone formation. In this study, we demonstrated that under sialoscintigraphic evaluations, the spontaneous secretion of the contralateral submandibular gland from patients with unilateral submandibular sialolithiasis was decreased compared to our baseline individuals who have no obstructive submandibular diseases. The findings are compatible with the previously known neuro-exocrine etiology in the development of sialolithiasis and reveal that this reduced salivary flow might occur in some individuals without the influence of surgery (parasympathectomy) or medications. To the best of our knowledge, this is the first study in which a decreased secretory function of a salivary gland by nature was proposed as a predisposing factor in the development of sialolithiasis.

Table 2: Comparison of the slope difference at the steady ascending phase using sialoscintigraphic curves

| Patient group | Uni- or bilateral parotid obstructive sialadenitis (n = 35) | p value |
|---------------|----------------------------------------------------------|---------|
| Unaffected side of submandibular gland | Bilateral submandibular glands | |
| Slope difference | 0.11 (0.31) | 0.55 (0.72) | .002* |
| Bilateral parotid glands | Unaffected side of parotid glands | |
| Slope difference | 0.24 (0.31) | 0.36 (0.51) | .352 |

Note: Values are means (standard deviation) for the quantitative variables. *Statistical significance (p < .05).
also noticed that spontaneous secretion was more frequent in one submandibular gland than in the contralateral gland in two subjects. In Aung’s study, when the researcher observed the time-activity curves of sialoscintigraphy, they also found that the parotid gland curves showed monotonic uptake until stimulation (limited spontaneous secretion), and the submandibular curves showed spontaneous secretion. This phenomenon also reflects the fact that in the unstimulated state, the contribution to all mouth saliva volume is approximately 60% from the submandibular glands and 25% from the parotid glands, and upon stimulation, the parotid glands account for at least 50% of all saliva volume, suggesting that the submandibular gland is responsible for the baseline saliva output under no stimulation in which a spontaneous secretion mechanism plays an important role. While the phenomenon of spontaneous secretion and higher incidence of sialolithiasis coexist in submandibular glands, the decreased spontaneous secretion shown through sialoscintigraphy in our study might be one of the contributing factors in the development of submandibular stones.

Readers may wonder whether the impaired spontaneous secretion on the contralateral side of submandibular glands can be used to explain the affected side. Previous research revealed that the salivary flow rates vary widely between subjects, but each individual’s flow rate remains relatively constant. Besides, one study enrolled 17 normal subjects receiving sialoscintigraphy found that the time-activity curves of right and left glands were generally symmetric, both in amplitude and time of maximum uptake. Thus a relatively parallel bilateral salivary flow within each individual may be assumed. However, Malpani et al., in 1995 disclosed that continuous, discrete, or mixed types of spontaneous secretion exist in submandibular glands in different individuals, and more times of unstimulated secretion in one side of submandibular gland than the other were identified in two out of 14 total subjects. Still, little is known about the intra-individual differences in submandibular spontaneous secretion, and further investigations are warranted.

After successful sialolith retrieval through gland-preserving management, studies have shown the possibility for the affected glands to return to normal function, although some chronically impacted submandibular glands may only restore excretory capability partially. The incidence of sialolithiasis recurrence in the diseased gland after gland-sparing lithotripsy remains unclear, ranging from 1.9% to 8.9% in previous reports. Whether decreased spontaneous secretion may predispose these suboptimally functioning submandibular glands at risk of recurrent stones or infection still needs to be investigated along with other possible factors on a larger scale, and to determine whether gland-sparing management is less likely to succeed in specific patient populations.

One study showing that sialodochoplasty and transoral sialolithotomy for submandibular sialolithiasis did not affect the rate of symptom or stone recurrence also supports our finding that the problem leading to recurrence is not related to the downstream resistance of the salivary ductal system. It should be noted that in our study that despite a reduced salivary secretion, no sialolith was present on the contrary side. It might be that all bilateral obstructive disease patients were excluded from the study and the computed tomography failed to detect the asymptomatic micro-sized stones. However, it can also reflect the fact that bilateral submandibular sialolithiasis is not common and often regarded as being predisposed by systemic factors or medications. In this case, the reduced salivary secretion might only serve as a predisposing component in the future development of sialolithiasis of the contralateral unaffected submandibular gland.

As the spontaneous secretion function of the submandibular gland declines, the importance of gland massage is primarily addressed. Traditionally, salivary gland massage can be applied under various conditions, including sialoadenitis and sialolithiasis. Gland massage also effectively prevents salivary gland dysfunction during high-dose radioactive iodine therapy for thyroid cancer. Contents in the salivary gland are shown to be effectively “emptied” by the massage maneuver. Little has been addressed regarding applying gland massage in preventing the development of sialolithiasis. It is possible that applying gland massage in these patients might compensate for the decreased spontaneous secretion and lead to a decreased recurrence rate. The maneuver can also be considered to be applied to the contralateral submandibular gland even without the presence of disease, as spontaneous secretion is also decreased. Moreover, in patients whose spontaneous secretion of the submandibular gland is suspected to be impaired, beverages containing caffeine or drugs, such as alpha-receptor antagonists, amphetamines, anticholinergics, antidepressants, antihistamines, antihypertensives, and antipsychotics, such as phenothiazines, should be avoided unless necessary, as these patients might be more vulnerable to these pharmacological effects.

There are several limitations to this study. First, the case number in this study is relatively limited and might contribute to particular bias in the results. Second, the study is based on sialoscintigraphy findings, and it needs to be correlated with the actual saliva production of the gland. Third, although none of the enrolled patients in this study were taking medication that would influence salivary flow, the amount of coffee consumed in these patients could not be accurately addressed and, thus, might have contributed to a particular bias. However, we believe it would have a limited impact on the scintigraphic results. These patients were instructed to avoid caffeine intake at their initial visit, allowing at least a 1-week period without possible influences before sialoscintigraphic examinations.

The gland function compensation by uninvolved gland should also be addressed. It is reported that in cases with unilateral parotid gland agenesis, most of these subjects presented with a painless swelling of the contralateral parotid gland or facial asymmetry without other significant clinical symptoms comprehended as compensatory functional hypertrophy. However, Chung et al. reported cases with the absence of the submandibular gland and the enlargement of the ipsilateral sublingual gland, and the authors stated that aplasia or atrophy of the submandibular gland is thought to cause hypertrophy of other glands, but the compensation of function by the glands has not been shown. Also, Li et al. reported that no overcompensation effect was measured in the opposite uninvolved parotid gland in head and neck cancer patients who were irradiated with the affected side parotid gland more functionally impaired. Based on these findings, we believe...
the phenomenon of the contralateral uninvolved salivary gland compensating for the compromised function of the involved gland remains limited and would not have influenced the findings in our study. Further studies are needed, as this preliminary scintigraphic study only indicates that the unaffected contralateral gland shows decreased spontaneous secretion in patients with unilateral submandibular gland sialolithiasis. Suppose the findings of decreased spontaneous secretion are associated with the development of submandibular gland sialolithiasis. In that case, the detailed mechanism should be further explored, as a decrease in saliva secretion might contribute to a decreased secretory neurotransmitting signal and impaired glandular secretory function. Additionally, the significance of this phenomenon needs to be further explored, as the formation of sialolithiasis appears to be multifactorial. The decreased spontaneous secretion must have worked with other predisposing factors together in the pathogenesis of sialolithiasis.

Based on these preliminary data, we recommend that physicians pay more attention to the sialoscintigraphy curve pattern in patients with obstructive submandibular sialoadenitis to evaluate the spontaneous secretion ability in these patients. The presence of decreased spontaneous secretion might provide helpful information in encouraging patients to perform gland massage more extensively, determining the need for close or regular follow-up, or in some extreme cases, deciding whether the submandibular gland should be preserved.

6 | CONCLUSION

Under sialoscintigraphic evaluations, the spontaneous secretion of the submandibular gland from patients with submandibular sialolithiasis is decreased compared to those without it, which might be associated with the development of sialolithiasis in the submandibular gland.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Farneti P, Macrì G, Gramellini G, Ghirelli M, Tesei F, Pasquini E. Learning - curve in diagnostic and interventional sialendoscopy for obstructive salivary diseases. Acta Otorhinolaryngol Ital. 2015;35(5):325-331.
2. Sroka R, von Holzschuher V, Zengel P, Schrötzlmaier F. Laser lithotripsy of salivary stones. In: Wang BJF, ligner J, eds. Biomedical Optics in Otorhinolaryngology: Head and Neck Surgery. Springer New York: 2016:155-166.
3. Pedersen AML, Sørensen CE, Proctor GB, Carpenter GH, Ekström J. Salivary secretion in health and disease. J Oral Rehabil. 2018;45(9):730-746.
4. Aiyetkomogbon JO, Babatunde LB, Salam AJ. Submandibular sialolithiasis: the roles of radiology in its diagnosis and treatment. Ann Afr Med. 2018;17(4):221-224.
5. Ko CW, Lee SP. Gallstone formation: local factors. Gastroenterol Clin North Am. 1999;28(1):99-115.
6. Dawes C. Factors influencing salivary flow rate and composition. In: Edgar WE, O'Mullane DM, eds. Saliva and Oral Health. 2nd ed. British Dental Association; 1996.
7. Anjos DA, Etchebehere ECSC, Santos AO, et al. Normal values of [99mTc]pertechnetate uptake and excretion fraction by major salivary glands. Nucl Med Commun. 2006;27(4):395-403.
8. Enfors BO. The parotid and submandibular secretion in man. Quantitative recordings of the normal and pathological activity. Acta Otolaryngol Suppl. 1962;172:1-67.
9. Malpani BL, Jaiswar RK, Samuel AM. Noninvasive scintigraphic method to quantify unstimulated secretions from individual salivary glands. Auris Nasus Larynx. 1999;26(4):453-456.
10. Malpani BL, Samuel AM, Ray S. Differential kinetics of parotid and submandibular gland function as demonstrated by scintigraphic means and its possible implications. Nucl Med Commun. 1995;16(8):706-709.
11. Hermann GA, Vivino FB, Shnier D, Krumm RP, Mayrin V, Shore JB. Variability of quantitative scintigraphic salivary indices in normal subjects. J Nucl Med. 1998;39(7):1260-1263.
12. Aung W, Murata Y, Ishida R, Takahashi Y, Okada N, Shibuya H. Study of quantitative oral radioactivity in salivary gland scintigraphy and determination of the clinical stage of Sjogren’s syndrome. J Nucl Med. 2001;42(1):38-43.
13. Harrison JD. Causes, natural history, and incidence of salivary stones and obstructions. Otolaryngol Clin North Am. 2009;42(6):927-947.
14. Schapher M, Koch M, Weidner D. Neutrophil extracellular traps promote the development and growth of human salivary stones. Cell. 2020;9(9):2139.
15. Li Y, Taylor JMG, ten Haken RK, Eisbruch A. The impact of dose on parotid salivary recovery in head and neck cancer patients treated with radiation therapy. Int J Radiat Oncol Biol Phys. 2007;67(3):660-669.
16. Upadhaya A, Meng Z, Wang P, et al. Effects of first radioiodine ablation on functions of salivary glands in patients with differentiated thyroid cancer. Medicine (Baltimore). 2017;96(25):e7164.
17. Chen YC, Han DY, Chang CC, Su CH, Hung SH, Hsu CH. The establishment and application of sialoscintigraphic reference values from patients with obstructive sialadenitis. Nucl Med Commun. 2020;41(4):308-313.
18. Chen YC, Dang LH, Chen LC, et al. Office-based salivary gland ductal irrigation in patients with chronic sialoadenitis: a preliminary study. J Formos Med Assoc. 2021;120(1 Pt 2):318-326.
19. Koch M, Zenk J, Iro H. Algorithms for treatment of salivary gland obstructions, Otolaryngol Clin North Am. 2009;42(6):1173-1192.
20. Stack BC Jr, Norman JG. Sialolithiasis and primary hyperparathyroidism. OJR Otorhinolaryngol Relat Spec. 2008;70(5):331-334.
21. Westhofen M, Schafer H, Seifert G. Calcium redistribution, calcification and stone formation in the parotid gland during experimental stimulation and hypercalcaemia. Cytochemical and X-ray microanalytical investigations. Virchows Arch A Pathol Anat Histopathol. 1984; 402(4):425-438.
22. Marchal F, Kurt AM, Dulguerov P, Lehrmann W. Retrograde theory in sialolithiasis formation. Arch Otolaryngol Head Neck Surg. 2001;127(1):66-68.
23. Teymoortash A, Wollstein AC, Lippert BM, Peldszus R, Werner JA. Bacteria and pathogenesis of human salivary calculi. Acta Otolaryngol. 2002;122(2):210-214.
24. Huoh KC, Eisele DW. Etiologic factors in sialolithiasis. Otolaryngol Head Neck Surg. 2011;145(6):935-939.
25. Kraaij S, Karagözoglu KH, Forouzanfar T, Veerman ECL, Brand HS. Salivary stones: symptoms, aetiology, biochemical composition and treatment. Br Dent J. 2014;217(11):E23.
26. Fry R, Singh KI, Das H, Singh K. Surgical management of sialolithiasis: a case report. Int J Curr Res Med Sci. 2018;4(3):113117.

27. Ship JA, Nolan NE, Puckett SA. Longitudinal analysis of parotid and submandibular salivary flow rates in healthy, different-aged adults. J Gerontol A Biol Sci Med Sci. 1995;50(5):M285-M289.

28. Schneyer LH, Levin LK. Rate of secretion by individual salivary gland pairs of man under conditions of reduced exogenous stimulation. J Appl Physiol. 1955;7(5):508-512.

29. Akker HPVD. Aspects of Salivary Gland Scintigraphy with 99mTc-Per-technetate. Amsterdam University; 1988.

30. Pedersen AML, Sørensen CE, Proctor GB, Carpenter GH. Salivary functions in mastication, taste and textural perception, swallowing and initial digestion. Oral Dis. 2018;24(8):1399-1416.

31. Ericsson Y, Hardwick L. Individual diagnosis, prognosis and counselling for caries prevention. Caries Res. 1978;12(Suppl 1): 94-102.

32. Yoshimura Y, Morishita T, Sugihara T. Salivary gland function after sialolithiasis: scintigraphic examination of submandibular glands with 99mTc-pertechnetate. J Oral Maxillofac Surg. 1989;47(7):704-710; discussion 710-1.

33. Su YX, Xu JH, Liao GQ, et al. Salivary gland functional recovery after sialendoscopy. Laryngoscope. 2009;119(5):1027-1032.

34. Makdissi J, Escudier MP, Brown JE, Osailan S, Mcgurk M. Glandular function after intraoral removal of salivary calculi from the hilum of the submandibular gland. Br J Oral Maxillofac Surg. 2004;42(6):538-541.

35. Park JH, Kim JW, Lee YM, Oh CW, Chang HS, Lee SW. Long-term study of sialodochoplasty for preventing submandibular sialolithiasis recurrence. Clin Exp Otorhinolaryngol. 2012;5(1):34-38.

36. Chung MK, Jeong HS, Ko MH, et al. Pediatric sialolithiasis: what is different from adult sialolithiasis? Int J Pediatr Otorhinolaryngol. 2007;71(5):787-791.

37. Lustmann J, Regev E, Melamed Y. Sialolithiasis. A survey on 245 patients and a review of the literature. Int J Oral Maxillofac Surg. 1990;19(3):135-138.

38. Trujillo O, Drusin MA, Rahmati R. Rapid recurrent sialolithiasis: altered stone composition and potential factors for recurrence. Laryngoscope. 2017;127(6):1365-1368.

39. Kraaj S, Karagözoglu KH, Kenter YAG, pijpe J, Gilijamse M, Brand HS. Systemic diseases and the risk of developing salivary stones: a case control study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;119(5):539-543.

40. Dellic K, Spijkervet FK, Vissink A. Salivary gland diseases: infections, sialolithiasis and mucoceles. Monogr Oral Sci. 2014;24:135-148.

41. Son SH, Lee CH, Jung JH, et al. The preventive effect of parotid gland massage on salivary gland dysfunction during high-dose radioactive iodine therapy for differentiated thyroid cancer: a randomized clinical trial. Clin Nucl Med. 2019;44(8):625-633.

42. Hong CM, Son SH, Kim CY, et al. Emptying effect of massage on parotid gland radioiodine content. Nucl Med Commun. 2014;35(11):1127-1131.

43. Soman B, Bhatnagar S. Adverse effects of drugs on salivary glands. Int J Dent Med Res. 2014;1(4):94-98.

44. Teymoortash A, Hoch S. Congenital unilateral agenesis of the parotid gland: a case report and review of the literature. Case Rep Dent. 2016;2016:2672496.

45. Chung J, Lee YW. Functional compensation of a hypertrophied sublingual gland and the absence of the ipsilateral submandibular gland. Br J Oral Maxillofac Surg. 2019;57(8):813-816.