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Association of serum electrolytes and smoking with salivary gland stone formation

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Abstract

To further define potential factors that may contribute to stone formation in salivary glands (sialolithiasis), a retrospective chart review was performed of patients diagnosed with sialolithiasis between March 1, 1998 and February 29, 2012. Information on salivary gland stone number, location, and size, medical history, medications, and serum electrolyte levels were collected. Associations between electrolyte levels and stone characteristics (such as stone number and size) were examined. Fifty-nine patients were identified; their median age was 58 years (range 25–89 years) and most were male (95%). Salivary stones were most commonly located in the submandibular glands (83%). Thirty-five patients (59%) had a smoking history, with 16 (27%) reported as current smokers. There was a significant association between current smoker status and stone size (mean largest stone size 12.4 ± 8.8 mm vs. 7.5 ± 4.8 mm in current smokers vs. non-smokers; $P = 0.03$). Serum sodium levels ($r = 0.32$, $P = 0.014$) and serum potassium levels ($r = 0.31$, $P = 0.017$) showed significant positive correlations with stone size. While the etiology of sialolithiasis remains unclear, smoking (which can contribute to reduced saliva flow) and higher serum sodium levels (which can reflect volume depletion) are associated with larger salivary stones.

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Competing interests

There are no competing interests or conflicts of interest.

Ethical approval

Approval was granted by the Washington, DC Veteran Affairs Medical Center (DCVAMC) Institutional Review Board (IRB) for this retrospective case study.

Patient consent

Not required.

Keywords

sialolithiasis; patient factor; smoking; diuretics; serum electrolyte levels

Introduction

Sialolithiasis is a common salivary gland dysfunction due to stone formation, occurring mostly in the submandibular salivary glands¹. Stone formation in the salivary gland can lead to recurrent pain and infection. The majority of patients for whom the stone cannot be removed or destroyed inside, require surgical excision of the salivary gland². However, these surgeries are done under general anesthesia and place branches of the facial nerve, hypoglossal nerve, and lingual nerve at risk³. Understanding the pathophysiology of stone formation may help to prevent stone formation and allow patients to avoid invasive surgical procedures.

Although the etiology and pathogenesis of sialolithiasis is not clear, several theories have been proposed from the analysis of extracted stones^{4,5}. Generally, the composition of a salivary stone contains both organic and inorganic components. The organic substances comprise cellular debris, glycoproteins, and mucopolysaccharides and the inorganic outer layer can be made up of calcium carbonates and phosphates^{6,7}. Salivary stasis, or even decreased salivary flow, has been indicated as a contributing factor to the development of salivary stones^{7,8}.

Additionally, inflammation, or sialadenitis, has been associated with the formation of salivary stones^{9,10}. Patient factors, such as tobacco smoking, reduced fluid intake, and the use of medications that diminish salivary output, have already been proposed to influence the salivary flow rate and inflammation in salivary glands^{4,9}. Interestingly, when compared to normal individuals, the stasis of salivary flow has also been found in alcoholic individuals, due to histopathological changes in serous acini from major and minor salivary glands¹¹.

Additionally, decreased salivary flow, or salivary stasis, can contribute to the formation of salivary stones through the accumulation of ions that have a role in the precipitation, accumulation, and aggregation of salivary stones; for example, salivary stasis has been shown to contribute to the precipitation of calcium (Ca^{2+})¹². Although the concentration of electrolytes such as Ca^{2+} in saliva has been shown to be directly associated with stone formation¹³, there is a lack of information on serum electrolyte levels. Thus, the serum concentrations of particular electrolytes, which might influence their salivary levels¹⁴, require investigation.

Accordingly, the present study was performed to analyze some of the common patient factors (such as tobacco smoking and alcohol use) and the serum electrolyte levels that may be associated with the size and number of salivary gland stones, using retrospective data from salivary stone patients.

Materials and methods

A retrospective chart review was performed to identify all patients seen with a diagnosis of sialolithiasis between March 1, 1998 and February 29, 2012 (*International Classification of Diseases, Ninth Revision*, ICD-9, 527.5). To identify patients with a diagnosis of sialolithiasis, all charts were meticulously reviewed and any patient found not to have salivary stones on imaging or direct visualization by an oral surgeon or otolaryngologist was excluded.

Information was then gathered with regards to demographics (age at time of chart review and sex), number of stones, stone location and size, medical history, medications, and serum electrolyte levels. For patients with multiple stones, the size of the largest stone was also recorded. Current use of alcohol and current smoking were recorded as smoking or alcohol consumption at or near the time of diagnosis; smoking history and history of alcohol use were recorded as any smoking or alcohol use now or in the past. The serum electrolyte levels obtained closest to the time of diagnosis were recorded: sodium (Na^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), potassium (K^+), chloride (Cl^-), bicarbonate (HCO_3^-), and phosphate (PO_4^{3-}). Patient medications were also recorded, such as diuretics, antihistamines, and antidepressants.

Data were recorded in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). The statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). Between-group comparisons were made using the binomial test, Fisher's exact test, the χ^2 test, or the independent samples *t*-test. Statistical comparisons between the study cohort and population figures for smoking were completed using χ^2 analysis with Yates' correction. Associations between two continuous variables were examined using Pearson correlation. A *P*-value of less than 0.05 was considered to be statistically significant.

Results

In total, 59 patients with salivary gland sialolithiasis were identified. Within this population, there were 56 men (95%) and three women (5%) ($P < 0.0001$ for equal proportions). The median age of the cohort was 58 years (range 25–89 years). Within the cohort, 45 patients (76%) had one stone and 14 patients (24%) had more than one stone ($P < 0.0001$ for equal proportions). Fourteen patients (24%) were found to be using diuretics, with hydrochlorothiazide and furosemide being the most frequently used. Fifty-three patients (90%) had a history of sialadenitis; the history of sialadenitis was unknown for six (10%) patients. Consistent with past studies^{7,15}, the most common stone location was found to be the submandibular salivary gland (83%; Table 1). Among the 49 patients with submandibular sialolithiasis, 47 were men and two were women. Salivary stones were found in the left submandibular gland in 18 patients (37%) and in the right submandibular gland in 28 patients (57%); three patients (6%) had bilateral disease. The difference between left and right laterality was not significantly different from 50% ($P = 0.18$).

Smoking history was positive in 35 (59%) subjects, negative in 20 (34%), and unknown in four (7%). Current smoking was positive in 16 (27%), negative in 39 (66%), and unknown in

four (7%). A positive history of alcohol use was found in 30 patients (51%); 25 patients denied using alcohol (42%) and four subjects (7%) had an unknown alcohol use history. Twenty-three patients (39%) were current alcohol users and 30 patients (51%) denied using alcohol; the current alcohol use status was unknown for six patients (10.2%).

To determine the predisposition of reduced salivary flow due to salivary gland infection/inflammation caused by smoking or alcohol use⁹, the associations of stone size with current alcohol use, history of alcohol use, smoking history, and current smoking was examined using analysis of variance; patients for whom the current or historical smoking or alcohol status was unknown were excluded. There was no significant association for stone size among patients who had a smoking history and those who did not. Interestingly, the stones of patients who were current smokers were significantly larger than those of patients who were not current smokers ($P=0.03$), with a mean of 12.4 and 7.5 mm, respectively. Alcohol use (current or prior) and diuretic use were not significantly correlated with stone size (Table 2).

A χ^2 analysis with Yates' correction was used to determine whether there was an association between the number of stones (1 vs. >1) among diuretic users, or confirmed smoking or alcohol use (current and history), excluding subjects with unknown smoking or alcohol status. No significant difference was found for each of these comparisons. Among diuretic users, five (36%) developed more than one stone, as did nine (20%) of those who were not taking diuretics. Among patients with a smoking history, seven (20%) developed more than one stone, as did seven (35%) of those who had never smoked ($P=0.22$). Among current smokers, four (25%) had more than one stone, as did 10 non-smokers (26%) ($P=0.99$). Of those with a history of alcohol use, seven (23%) developed more than one stone, as did seven (28%) of those who had never used alcohol ($P=0.69$). Among current alcohol users, six (26%) developed more than one stone, as did seven (23%) of the non-alcohol users ($P=0.82$).

The serum electrolyte levels of all patients in the cohort were examined and investigated for any associations with stone size using Pearson correlation. Interestingly, serum Na^+ ($r=0.32$; $P=0.014$) and serum K^+ ($r=0.31$; $P=0.017$) were found to have a significant positive correlation with stone size (Table 3). All other comparisons were not significant. Further analysis determined a significant association between serum K^+ levels (mean $\pm$ standard deviation) and the number of stones. A lower serum K^+ level was significantly associated with having more than one stone (mean serum K^+ , 4.2 ± 0.5 mEq/l vs. 3.8 ± 0.4 mEq/l in subjects with one stone vs. more than one stone, respectively; $P=0.0064$) (Table 4).

Discussion

Sialolithiasis or salivary stone disease is a major cause of salivary gland dysfunction¹⁵, yet the etiology remains unclear. This retrospective study, examining multiple patient factors thought to be related to stone formation, sought to improve our understanding of the etiology and pathogenesis of sialolithiasis.

Consistent with earlier findings, most cases of salivary stones were found in the submandibular glands^{7,15}. The primary reason for this could be physiological: the submandibular gland has a long duct with two bends, traveling upward and forward, and then initiates a radical turn towards the hilus of the gland^{16,17}. The salivary flow in the duct against gravity results in saliva stagnation, or 'salivary stasis'. Additionally, the relatively narrower tubule in Wharton's duct of the submandibular gland than in Stensen's duct of the parotid gland also contributes^{16,17}. The higher viscosity of submandibular saliva than parotid saliva increases the likelihood of hydroxyapatite calculi and stone formation. In addition, calculus clearance is facilitated by improved salivary clearance at the parotid duct through its horizontal path (slope)^{2,18,19} and a less viscous saliva is produced in the parotid duct than in the submandibular duct^{20,21}.

The formation of salivary stones has been associated with decreased salivary flow and inflammation in the salivary glands and ducts²². Tobacco smoke has been linked to diminished salivary output²³ and may predispose the salivary glands and ducts to inflammation¹². Thus an investigation was performed to determine whether smokers in the present study cohort (those who currently smoked and those with a history of smoking) developed a greater number of stones or stones of a greater size among patients with sialolithiasis. A significant association between smoking and the size of the stone was revealed, and it was found that current smokers had larger stones than those who had stopped smoking.

The reason for this may be two-fold. First, a recent clinical study showed that the long-term effects of tobacco use lead to a reduced whole-mouth salivary flow rate²³. Indeed, decreased salivary gland secretion has been proposed to be the first step in salivary stone formation¹⁰. Thus, persistent smoking may further decrease salivary flow, exacerbating the effects of decreased salivary output and subsequently contribute to stone growth. Second, smoking may lead to an increase in bacterial load in the salivary duct or gland by decreasing the antimicrobial activity of the saliva¹². Indeed, bacteria may play a role in the pathogenesis of sialolithiasis²⁴. It has been proposed that, during secretory inactivity, microbes may ascend the main salivary duct and proliferate¹⁰. Thus, by decreasing the antimicrobial activity of saliva, continued smoking can contribute further to the development of sialolithiasis by allowing an increased amount of microbes to enter the salivary ducts, leading to inflammation and fibrosis that may compress the large ducts¹⁰, and contributing further to the nucleation, retention, and growth of hydroxyapatite^{4,9}.

Additionally, decreased salivary flow, or salivary stasis, may contribute to the precipitation, accumulation, and aggregation of salivary stones; indeed, salivary stasis contributes to the precipitation of calcium¹². Although the saliva electrolyte concentration, such as that of Ca^{2+} , has been associated with stone formation, there is a lack of information on serum electrolyte levels¹³. Thus serum electrolyte levels, which might influence the salivary electrolyte content¹⁴, were investigated in the present study.

The composition of the saliva in the salivary duct is dependent on the ion transport across the epithelia²⁵. Thus, the final composition is dependent upon the secretory status of the salivary duct cells and the normal functionality of various transporters located across the

apical and basolateral membrane. Accordingly, the results of the present study, which showed that a higher serum K^+ level was significantly associated with having only one stone, are interesting. Under normal conditions, serum K^+ is secreted across the basolateral membrane through channels such as the $Na^+-K^+-ATPase$ that are utilized to energize voltage-dependent transport processes, for example basolateral HCO_3^- uptake, luminal HCO_3^- exit, and luminal Na^+ uptake²⁵. Thus, changes in serum K^+ levels may affect the mechanism of the basolateral primary $Na^+-K^+-ATPase$ and disrupt the electrogenic gradient needed for secondary active transport mechanisms that mediates the properties of the saliva, such as pH and Na^+ ion concentration²⁶. These changes may predispose salivary conditions to prevent the accumulation of stones.

The most significant finding of this study is that both Na^+ and K^+ serum levels had a positive correlation with the stone size in sialolithiasis patients. This makes sense, as both electrolytes play important roles in transepithelial ion transport across salivary gland ductal cells. Indeed, the homeostasis of the Na^+ and K^+ gradients through the basolateral primary $Na^+-K^+-ATPase$ is key to the transport of other ions across the apical and basolateral membranes of the cell²⁶. For example, in normal salivary ductal cells, the basolateral $Na^+-HCO_3^-$ co-transporters utilize the Na^+ gradient to transport HCO_3^- in and protons out of the duct²⁶; these have been proposed to be a part of a ductal HCO_3^- -regulating complex to maintain acidic saliva²⁷. Thus, the disruption of this HCO_3^- could cause aberrant HCO_3^- secretion and increase the alkalinity of the saliva, which may predispose to the continued accumulation of calcium phosphate deposits, leading to larger stones.

Moreover, while the etiology of sialolithiasis remains unclear, the higher serum Na^+ level may reflect systemic volume depletion. However, it is not clear to what extent such changes in serum Na^+ levels may contribute to reduced saliva secretion in humans, which is considered a factor for stone formation^{7,8}. Additionally, it has been proposed that the submandibular duct has ion transport pathways that are sensitive to the extraluminal concentrations of potassium²⁸, so changes in serum K^+ may impact HCO_3^- transport across ductal epithelia, and a resulting rise in saliva pH could create a favorable condition for calcium phosphate precipitation similar to calcium phosphate kidney stone formation²⁹. However, the formation of such stones is multifactorial and is not dependent on a singular cause, and, particularly in sialolithiasis patients, the disruption of normal conditions due to a stone may lead to several abnormal outcomes. It is possible, then, that higher serum K^+ levels may directly lead to increased stone size while indirectly decreasing stone number by modulating the circumstances in which stones accumulate. Or, higher serum K^+ may directly decrease the number of stones, while indirectly changing the environment to intensify the aggregation of smaller stones to form larger stones. Thus, the impact of serum K^+ is interesting and deserves further research to determine its direct and indirect impact on the conditions for salivary stone formation.

This study demonstrated a possible association between smoking and salivary stone disease. Moreover, a significant correlation between certain serum electrolytes and (1) stone size, and (2) the number of stones was found. Future research in this area should attempt to delineate the importance of both serum and saliva electrolyte levels in salivary stone formation. Prospective studies should involve the collection and analysis of saliva and serum in patients

with stones. Further insight will also be gained by examining how serum Na^+ and serum K^+ levels influence Ca^{2+} transport within the ductal lumen by measuring those ions in saliva.

Although there is substantial information gained from the present study that may be used to propose future research, there are some limitations. First this study was conducted at the Washington, DC Veterans Affairs Medical Center, which inevitably may be VA-centric, and which also has a greater male patient population. Moreover, the discussion on serum electrolytes assumes that all other serum electrolyte levels remain the same except for the ones being discussed. Indeed, the molecular mechanisms of cellular ion transport are complex, and mechanisms are at work to ensure that sudden and short-term changes to the electrolyte levels have no long-term effect. It is acknowledged that the addition of saliva electrolyte data would have provided important information when determining the association of serum electrolyte levels with salivary gland stone formation. Since this was a retrospective chart review in which saliva specimens were not collected and analyzed, the serum electrolyte data were used to uncover the unknown factors that might be associated with salivary stone formation using the existing knowledge on salivary ductal ion transport and other factors predisposing to salivary stone formation. It is expected that the findings of the present study will help in the planning and execution of future prospective clinical research.

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Table 1

Overall cohort characteristics.

	No. (%)
Sex	
Male	56 (95)
Female	3 (5)
Total	59
	($P < 0.0001$ for equal proportions) ^a
No. of stones	
1	45 (76)
>1	14 (24)
Total	59
	($P < 0.0001$ for equal proportions) ^a
Diuretic use	
No	45 (76)
Yes	14 (24)
Stone location	
SMG	49 (83)
Parotid	8 (13)
Minor	1 (2)
SMG + parotid	1 (2)

SMG, submandibular gland.

^aBinomial test.

Table 2

Comparison of stone size among diuretic users, smokers, and alcohol users.

	Stone size (mm) Mean $\pm$ SD	P-value ^a
Diuretic user		0.98
No (<i>n</i> = 45)	9.0 $\pm$ 6.8	
Yes (<i>n</i> = 14)	9.0 $\pm$ 5.5	
Current smoker ^b		0.03
No (<i>n</i> = 39)	7.5 $\pm$ 4.8	
Yes (<i>n</i> = 16)	12.4 $\pm$ 8.8	
History of smoking ^b		0.46
No (<i>n</i> = 20)	7.5 $\pm$ 4.2	
Yes (<i>n</i> = 35)	9.8 $\pm$ 7.6	
Current alcohol user ^b		0.34
No (<i>n</i> = 30)	8.6 $\pm$ 6.3	
Yes (<i>n</i> = 23)	10.2 $\pm$ 7.4	
History of alcohol use ^b		0.73
No (<i>n</i> = 25)	8.6 $\pm$ 6.3	
Yes (<i>n</i> = 30)	9.5 $\pm$ 7.1	

SD, standard deviation.

^aAnalysis of variance.^bSubjects with unknown history and unknown current use were excluded from this analysis.

Table 3

Stone size comparison based on serum electrolyte measurements.

	Correlation with stone size ^a	P-value
Serum Na ⁺	0.32	0.014
Serum Ca ²⁺	-0.09	0.53
Serum Mg ²⁺	0.17	0.22
Serum K ⁺	0.31	0.017
Serum Cl ⁻	0.16	0.23
Serum HCO ₃ ⁻	-0.17	0.19
Serum PO ₄ ³⁻	0.14	0.31

^aPearson correlation.

Table 4

Comparison of the number of stones based on mean serum electrolyte levels.

	1 stone Mean $\pm$ SD	>1 stone Mean $\pm$ SD	<i>P</i>-value^a
Serum Na ⁺ (mEq/l)	139.2 $\pm$ 3.2	138.9 $\pm$ 3.4	0.75
Serum Ca ²⁺ (mg/dl)	9.2 $\pm$ 0.4	9.4 $\pm$ 0.5	0.25
Serum Mg ²⁺ (mEq/l)	2.1 $\pm$ 0.2	2.2 $\pm$ 0.2	0.59
Serum K ⁺ (mEq/l)	4.2 $\pm$ 0.5	3.8 $\pm$ 0.4	0.0064
Serum Cl ⁻ (mEq/l)	104.5 $\pm$ 3.0	102.6 $\pm$ 5.1	0.10
Serum HCO ₃ ⁻ (mEq/l)	26.4 $\pm$ 2.3	25.6 $\pm$ 3.3	0.33
Serum PO ₄ ³⁻ (mEq/l)	3.4 $\pm$ 0.7	3.5 $\pm$ 0.7	0.94

SD, standard deviation.

^a
t-test.