Systemic diseases and the risk of developing salivary stones: a case control study

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Objective. To investigate the possible relationship between the presence of salivary stones and systemic diseases, medication, smoking, and alcohol consumption.

Study Design. A retrospective, case control study. Medical records of patients with salivary stones and those of control patients without salivary stones were retrospectively reviewed. Data regarding the affected salivary gland, the presence of systemic disease, and the use of medication, tobacco, and alcohol were recorded. Statistical analysis was performed using the Fisher Exact tests.

Results. Medical records of 208 patients with salivary stones and those of 208 control patients were reviewed. Of the patients diagnosed with salivary stones, the submandibular gland was affected in 85.6% of the patients, the parotid gland in 9.6%, and the sublingual gland in 2.4% of the patients. None of the recorded systemic diseases was more prevalent in patients with salivary stones. Patients with salivary stones used significantly more antibiotics compared with the control group (P = .037). No significant differences were observed for other types of medication. There was no correlation between salivary stone formation, smoking, and alcohol consumption.

Conclusions. The present study suggested that systemic diseases, medication, smoking, and alcohol consumption play no or only a limited role in the onset of salivary stones. (Oral Surg Oral Med Oral Pathol Oral Radiol 2015;119:539-543)

Salivary stones occur as one or more calcified structures within the salivary ductal system. The formation of salivary stones, also known as sialoliths, can result in partial or total obstruction of the ductal system leading to recurrent swelling of the salivary gland, pain, and acute or chronic infection. The annual incidence of salivary stones is estimated between 1 per 15,000 and 1 per 30,000 individuals. Salivary stones occur most often in patients over 40 years of age and rarely in children. In studies published before 1990, a male predominance is evident. However, more recent studies have shown an almost equal distribution between males and females. More than half of the salivary stones have a diameter between 2.1 and 10 mm, and only 7.6% are larger than 15 mm in section.

Salivary stones are more often located within the ductal system of the submandibular gland (72%-95%) than in the ductal system of the parotid gland (4%-28%). Salivary stones are seldom found in the sublingual glands or accessory salivary glands. The higher incidence of salivary stones in the ductal system of the submandibular gland might be attributed to its longer duct, salivary flow against gravity, and a more alkaline saliva with a higher calcium and mucin content.

The cause of salivary stone formation remains unclear. However, there are two main theories that attempt to explain the formation of salivary stones. The first theory postulates that a local inflammatory process leads to calcification of a mucus plug. The second theory assumes that microsialoliths, produced by autophagosomes in the salivary gland, form a nidus for calcium precipitation.

Salivary stones are mainly composed of inorganic material, such as hydroxyapatite, carbonateapatite, whitlockite, and brushite, with smaller amounts of organic material, such as collagen, glycoproteins, lipids, and carbohydrates. Kidney stones mainly contain calcium oxalate, uric acid, struvite, cystine, and small amounts of phosphate and ammonium. The main components of gallstones are cholesterol, bilirubin, bile acids, calciumapatite, and small amounts of magnesium and struvite.

Statement of Clinical Relevance

The etiology of the development of a salivary stone is still not clear. We found that systemic diseases, medication, smoking, and alcohol consumption play no or only a limited role in the onset of salivary stones.
Some cases of individuals developing salivary stones concomitant with gallstones\textsuperscript{14} or kidney stones\textsuperscript{15} have been described. Conflicting data were obtained when this possible relationship was investigated in groups of patients with salivary stones. Lustmann and co-workers\textsuperscript{6} found an incidence of kidney stones of 10.7% in a group of 56 patients with salivary stone formation. This is higher than the incidence in the general population and suggests a relationship between salivary stone formation and nephrolithiasis. However, Zenk et al.\textsuperscript{10} did not find a higher prevalence of nephrolithiasis (2%) and cholelithiasis (1.6%) in a group of 635 patients with salivary stone formation compared with the general population. Huoh et al.\textsuperscript{16} retrieved data from the medical records of patients diagnosed with salivary stones at the University of California. They also did not find a higher prevalence of cholelithiasis in patients with salivary stone formation compared with the general population.

In the studies cited above,\textsuperscript{6,10,16} the incidence of systemic disorders in patients with salivary stone formation was compared with data on the prevalence of diseases in the general population obtained from other studies. To our knowledge, no case control studies have investigated the potential association between systemic disorders and the development of salivary stones. Therefore, we performed a case control study to explore the relationship between the onset of salivary stones and the presence of systemic diseases, use of medication, and lifestyle factors.

**MATERIALS AND METHODS**

A retrospective case control study was conducted. The study group consisted of patients with salivary stones who had undergone surgical removal of sialoliths in the VU University Medical Center Amsterdam, Catharina Hospital in Eindhoven and Onze Lieve Vrouwe Gasthuis in Amsterdam in The Netherlands from November 1, 2001, until December 31, 2013. All patients had been referred to the hospitals because of symptomatic salivary stones. A total of 208 medical reports of patients with salivary stones were available for analysis. Each patient with a salivary stone was matched with an age- and control-matched individual presenting at the same departments of Oral and Maxillofacial Surgery with medical problems other than a salivary stone.

The medical records of both the study patients and the matched control patients were systematically reviewed. The following clinical data were retrieved and processed anonymously into an Excel spreadsheet: the affected salivary gland and the presence of hyperthyroidism, diabetes, cardiovascular disease, hypertension, human immunodeficiency virus (HIV), tuberculosis, cholelithiasis, nephrolithiasis, cirrhosis, hepatitis, Parkinson disease, epilepsy, rheumatoid arthritis, Sjögren syndrome, gout, and malignancies. Data about medication use were obtained and categorized according to the Dutch national formulary (Pharmacotherapeutisch Kompas).\textsuperscript{17} The records were also analyzed for information about current use of tobacco, alcohol, or both. When data on smoking or use of alcohol were available in the patients’ records, these data were processed as yes/no.

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Inc., Armonk, NY), using the Fisher Exact two-sided tests. $P$ values less than .05 were considered significant.

**RESULTS**

A total of 208 patients with salivary stones, with 112 males (54%) and 96 females (46%) (male-to-female ratio: 1.17:1) and a mean age of 46.8 years (range 8-87 years), were identified. A case control group consisting of 208 patients, with 112 males and 96 females and a mean age of 46.4 years (range 8-88 years), was created. The submandibular gland was affected in 85.6% of the patients, the parotid gland in 9.6%, and the sublingual gland in 2.4%.

The prevalence of systemic diseases in both the patient group and the control group is presented in Table I. No relationship was found between salivary stone formation and most systemic diseases. However, the prevalence of cholelithiasis and Sjögren syndrome was almost significantly higher in the control group than in patients with salivary stones ($P = .061$).

There was a lack of data regarding smoking in 72% of the patients with salivary stone formation and in 51% of the control patients. In the available documents, however, there was a trend toward statistical significance ($P = .097$), with 49.2% smokers identified among 59 patients with salivary stone formation and 34.9% smokers among 106 control patients. Data regarding alcohol use were lacking in the records of 76% of the patients with salivary stone formation and 57% of the control patients. The available data did not show a significant difference in alcohol consumption between the 50 individuals with salivary stone formation (50%) and the 90 individuals from the control group (55.6%) ($P = .597$).

**DISCUSSION**

Several studies have investigated the possible relation between salivary stone formation and systemic diseases or use of medication. Lustmann and co-workers\textsuperscript{6} found an incidence of kidney stones of 10.7% in patients with salivary stone formation, which was considerably higher than the incidence in the general population. In our case control study, the prevalence of nephrolithiasis in the patient group did not differ from...
the prevalence in the control group. These results are similar to those in the studies of Zenk et al.\textsuperscript{10} and Huoh et al.,\textsuperscript{16} who reported prevalence rates of kidney stones comparable with those in the general population. This suggests that the risk factors for developing a salivary stone and a kidney stone are not related. An Italian study reported high prevalence rates of diabetes mellitus (25\%) and hypertension (20\%) in patients with salivary stone formation.\textsuperscript{4} However, in a subsequent study, the prevalence rates of hypertension and diabetes mellitus were comparable with the prevalence rate in the general population.\textsuperscript{10} In our case control study, we also observed no differences in the prevalence rates of hypertension and diabetes mellitus (see Table I).

Leung et al\textsuperscript{14} described a 49-year-old man with multiple salivary stones and a medical history of multiple gallstones. We observed a nonsignificant higher prevalence of cholelithiasis in the control group than in the patients with salivary stone formation (see Table I). In a previous study, the prevalence of cholelithiasis in a group of 635 patients with salivary stone formation was not higher than in the general population,\textsuperscript{10} which was confirmed by Huoh et al.\textsuperscript{16}

It is hypothesized that a decreased salivary flow rate may facilitate the formation of salivary stones.\textsuperscript{2} However, we did not find an increased prevalence of salivary stones in patients with Sjögren syndrome. The relatively high prevalence of Sjögren syndrome in control patients in the present study (see Table I), is probably explained by the fact that patients with a suspicion of Sjögren syndrome are frequently referred to Oral and Maxillofacial surgeons for further investigation and subsequently are overrepresented in the control group.

Two case reports suggested a possible relation between salivary stone formation and medication. Perrotta et al.\textsuperscript{18} described a 57-year-old woman with Parkinson disease and salivary stones in both the submandibular gland and the parotid gland and was treated with levodopa and amantadine. The authors suggested that the medication may have contributed to sialolith formation in this patient. Another case report\textsuperscript{19} described a 76-year-old woman with salivary stones in the submandibular glands and had a medical history of hypertension, a myocardial infarction 2 years earlier, and use of methyldopa.

Many types of medications, such as diuretics, antihistamines, antihypertensive drugs, antipsychotic medications, and antidepressants, decrease the salivary flow rate. The use of these medications could subsequently facilitate the formation of salivary stones.\textsuperscript{5} The use of diuretics in the cohort group of Huoh and co-workers\textsuperscript{16} was higher than in the general population. In the present case control study, the use of diuretics in patients with salivary stone formation was comparable with the control group.
(Table II). This is in agreement with the study by Zenk et al., where the use of diuretics by patients with salivary stones formation was comparable with that in the general population. Our case control study also confirms the finding in the study by Zenk et al. that the use of thyroid medications and antidiabetes medications by patients with salivary stone formation is comparable with that by individuals without a salivary stone.

The use of antibiotics was higher in the group of patients with salivary stone formation compared with the control group (see Table II). This may be related to the fact that salivary stone formation is frequently associated with sialadenitis. In many cases, the referring dentist or general practitioner may have prescribed antibiotics as initial treatment.

Huoh et al. found a higher rate of smoking in patients with salivary stones than in the general population, although the difference did not reach statistical significance. In our case control study, we observed a similar trend, with more smokers among patients with salivary stone formation, suggesting that smoking increases the risk of developing a salivary stone. Tobacco smoking can cause inflammation and the subsequent formation of a mucus plug and intraglandular concretion, which ultimately result in the formation of a salivary stone.

The mean age of the patients with salivary stone formation in the present study is comparable with that of previous studies. The distribution of salivary stones over the different salivary glands is also in accordance with previous reports. In the present study, a small male preponderance was observed, which is in agreement with the study of Zenk et al. Older studies found a more extensive male preponderance.

A potential limitation of the present case control study is the use of data from medical records, which had not specifically been recorded for scientific purposes. Incompleteness of information in medical history records is rather common. Another potential limitation is the hospital-based character of the study. The control patients also had been referred to the departments of Oral Maxillofacial Surgery for specific diseases, such as oral malignancies and Sjögren syndrome. This means that systemic factors that are associated with these oral diseases may have been overrepresented in the control group thereby obscuring the potential contribution of certain systemic factors in the development of salivary stones.

Despite these limitations, the data of the present case control study indicate that systemic diseases and use of medication do not play a prominent role in the development of salivary stones. This suggests that local factors, such as anatomic variations of the salivary ducts, an altered biochemical composition of saliva, or both are probably more important factors in the development of salivary stones.

REFERENCES


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