

Salivary stones: symptoms, aetiology, biochemical composition and treatment

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Salivary stones, also known as sialoliths, are calcified concretions in the salivary glands. Sialoliths are more frequently located in the submandibular gland (84%), than in the parotid gland (13%). The majority of the submandibular stones are located in Wharton's duct (90%), whereas parotid stones are more often located in the gland itself. Salivary stones consist of an amorphous mineralised nucleus, surrounded by concentric laminated layers of organic and inorganic substances. The organic components of salivary stones include collagen, glycoproteins, amino acids and carbohydrates. The major inorganic components are hydroxyapatite, carbonate apatite, whitlockite and brushite. The management of salivary stones is focused on removing the salivary stones and preservation of salivary gland function which depends on the size and location of the stone. Conservative management of salivary stones consists of salivary gland massage and the use of sialogogues. Other therapeutic options include removal of the stone or in some cases surgical removal of the whole salivary gland.

IN BRIEF

- Salivary stones or sialoliths are calcified concretions in the salivary glands, most frequently located in Wharton's duct of the submandibular gland.
- Salivary stones consist of a mineralised nucleus, surrounded by laminated layers of organic and inorganic substances.
- The management of salivary stones depends on the size and location of the stone.

INTRODUCTION

Salivary stones or sialoliths are calcified structures or concretions located in the parenchyma or ductal system of the salivary glands (Fig. 1). Sialolithiasis is a common salivary gland disorder characterised by the obstruction of the salivary secretion, accounting for approximately one third of salivary gland disorders.¹

Most cases of sialolithiasis present with symptoms such as pain and swelling in the submandibular or parotid region during mealtime (Table 1). Swelling is the most common symptom in submandibular stones, followed by pain. Three percent of the patients with a submandibular stone have no symptoms. Swelling is also the most common symptom of a parotid gland stone. Pain is present in approximately half of the patients with a parotid stone and only 1% has no symptoms.²⁻⁴ In general, pain and swelling are more pronounced when a stone is located in the duct than when the stone is located in the gland itself.²

Characteristics for sialolithiasis are episodes of pain and swelling during mealtime which may persist for a few hours, followed by long episodes of remission (weeks or months).^{2,5} The pain and swelling are caused by the obstruction of the salivary flow in the affected gland, resulting in accumulation of saliva and a subsequent increase in intraglandular pressure. In incomplete obstruction of the duct, saliva can seep through or around the sialolith. In these cases, a salivary stone can be symptomless and these stones may be an incidental finding on a dental panoramic radiograph.⁶

The duration of symptoms before patients present in a clinic varies considerably. The mean duration of symptoms is approximately five years and four months for submandibular stones and four years and ten months for parotid stones.⁷ One third of the patients with sialolithiasis will present within the first six months of symptoms.²

In 90% of the patients with a salivary stone, infection of the affected gland is present and in 12–18% a purulent discharge is seen.^{2,8,9}

The salivary flow rate of patients with sialolithiasis decreases when the mass of the sialolith increases. The mean submandibular salivary flow rate in patients with a submandibular stone was 38% lower compared to healthy individuals (0.18 and 0.29 ml/min, respectively).¹⁰ Nishi *et al.*¹¹ observed a mean reduction of 84% of the salivary flow rate of the affected submandibular gland compared to the unaffected contralateral gland.



Fig. 1 Fragmented sialolith, removed from the submandibular gland

Table 1 Frequency of swelling and pain in patients with salivary stones²⁻⁴

	Submandibular stone	Parotid stone
Swelling	86–92%	88–93%
Pain	35–47%	88–93%
No symptoms	3%	1%

Long-term obstruction of the salivary flow may increase intraglandular pressure, leading to destruction of the salivary gland and formation of connective tissue. Dissected submandibular salivary glands showed periductal and interlobular fibrosis, lymphocytic infiltration and atrophy of the acinar cells.¹²⁻¹⁴

Salivary stones usually have a yellow or yellow-brown colour, and vary greatly in size and weight. The weight of salivary stones varies from 1 mg to almost 6 g, with an average weight of 300 mg.¹⁵ Generally, submandibular stones are slightly larger than parotid stones (Table 2).^{3-5,16} Approximately 59% of the stones have a diameter between 2.1 and 10 mm and 7.6% are larger than 15 mm in section.¹⁷

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Salivary stones are classified as 'giant salivary stones' when the diameter is 15 mm or more in any direction or when the weight is 1 g or more. Giant salivary stones are usually located in the glandular parenchyma and are rarely found in Wharton's or Stenson's ducts.¹⁸

The shape of a salivary stone depends on the location from where the stone originates. Stones originating from the ductal system are mostly elongated, whereas stones originating from the hilus or gland are round or oval.^{1,2,17,19} Generally, submandibular stones have a smoother surface whereas parotid stones have a more irregular surface.³

Incidence and distribution between glands

The mean incidence of hospital admission for patients with symptomatic sialolithiasis in the United Kingdom is 27.5 per million per year, and the estimated prevalence of sialolithiasis is 0.45% in an average life expectancy of 76 years.¹⁶ This percentage is considerably lower than the previously reported 1.2% based on post-mortem research by Rauch and co-workers.²⁰

Sialolithiasis is most common in the fourth and fifth decade of life. The average age of patients with submandibular stones is slightly younger than that of patients with parotid stones (Table 2).^{2-4,21} Sialolithiasis in minor salivary glands seems to occur later in life, in the fifth to eight decades. Sialolithiasis in the first decade of life is rare, and encompassing 2.9% of all cases.¹⁷ Sialolithiasis is familial in approximately 1% of the cases.³ Bullock *et al.*²² reported on a family in which three successive generations (grandmother, mother and grandchild) had salivary stones in both submandibular and parotid glands.

Until the nineties of the last century, most studies reported a male predominance of sialolithiasis, varying from 2.5:1 to 1.2:1.^{2,8,17,23,24} However, more recent studies reported an almost equal distribution of salivary stones between men and women.^{16,25}

Salivary stones are equally distributed between the left and right side of the oral cavity.^{2,5,17,26,27} In 70–80% of the patients a single stone is found, in 20% two salivary stones are found and in roughly 5% three or more salivary stones are found in the affected salivary gland.¹⁷

The submandibular gland is affected in 72 to 95% of the cases, whereas the parotid gland is only affected in 4 to 28% of the patients. Salivary stones in the sublingual and minor salivary glands are rare, and comprises only 0.4 to 7% of all cases.^{2,3,5,17,20,25}

Submandibular stones are usually located in the duct (80–90%), of which 57% is located in the hilum and 34% is located in the distal duct. Ten percent of

the submandibular stones is located in the gland itself.^{3,28} Twenty-three percent of the parotid stones is located in the parenchymal system, 13% is located in the hilum and 64% is located in the distal duct.³

Sialoliths of the minor salivary glands are most frequently located in the upper lip (47%), the buccal mucosa (35%) and lower lip (10%). Only a few case reports described sialolithiasis of the minor salivary glands of the tongue and palate.^{1,12,21,29-31}

AETIOLOGY

The exact aetiology of salivary stones is not completely understood, and various hypotheses have been put forward. These hypotheses include the agglomeration of sialomicroliths, anatomical variations of the salivary ducts and an altered biochemical composition of saliva. It is considered that salivary stasis or decreased salivary flow contributes to the precipitation of calcium.¹⁴

Sialomicroliths

A sialomicrolith is a microscopic concretion in a salivary gland. These concretions consist of crystals containing calcium and phosphorus, as well as organic secretory material in granular form and necrotic cell residues.^{28,32} Sialomicroliths have been identified in serous acinar cells, striated ductal cells, lumen and interstitium of almost all normal submandibular glands and in 10–20% of the normal parotid glands.^{21,33-37} The observation that sialomicroliths were more frequently found in the submandibular gland may correspond to a higher calcium concentration in submandibular glands.³⁶ The size of microcalculi differs per place of origin; intracellularly sialomicroliths can be up to 25 µm, in acinar lumen up to 70 µm and interstitially up to 35 µm.^{14,33}

The incidence of sialomicroliths is related to the age of the patient, with an increased sialomicrolith formation in the intraglandular duct system of the submandibular gland in patients of 40 years or older.^{28,34} Secretory inactivity of a normal salivary gland also leads to increased formation of sialomicroliths.³⁶ Sialomicroliths usually form in autophagosomes in normal salivary glands, enter the lumen and pass from the salivary gland in the saliva unnoticed. Occasionally, the sialomicroliths might become impacted resulting in local microobstruction. This microobstruction may cause atrophic foci and chronic sialendinitis.^{1,33,34,38} These microobstructions may clump together into a salivary stone. However, the incidence of sialomicroliths is not related to the duration of symptoms of sialolithiasis.

Microorganisms

Microorganisms do not seem to play a

Table 2 Characteristics of submandibular and parotid sialoliths^{2-5,16,17,20,21,25}

	Submandibular stone	Parotid stone
Incidence	72–95%	4–28%
Average size	8.3 mm (2–30)	6.4 mm (4–15)
Average age	43 years (40.5–48)	49.8 years (47.8–52.6)

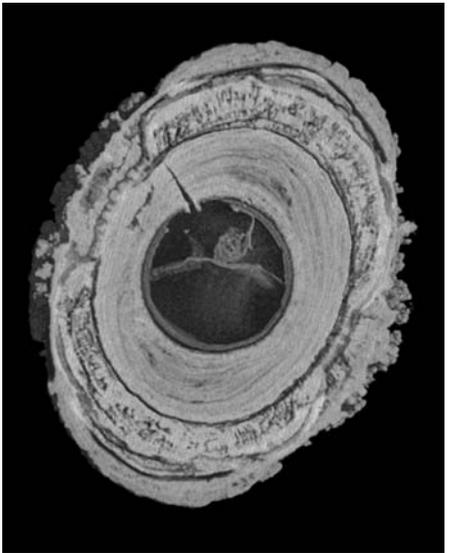


Fig. 2 Micro CT scan of a sialolith, showing an organic nucleus surrounded by laminated layers of organic and inorganic substances (courtesy of Professor Johan Aps, University of Washington, School of Dentistry)

significant role in the initiation of salivary stones, as very few studies identified microorganisms in the nuclei of sialoliths.^{31,39-42} However, in the intermediate and peripheral parts of sialoliths microorganisms have been identified, mostly oral commensal bacteria like *Streptococcus* or *Peptostreptococcus* species.^{14,29,39,43-46} The external surfaces of calculi removed from infected salivary glands, were found to be covered with a heavy accumulation of filamentous and rod shaped bacteria with a diameter of 0.5–1 µm.^{28,40,44}

Salivary gland anatomy

The anatomical differences between Wharton's and Stenson's duct may favour the formation of sialoliths in the submandibular gland. Although the diameter of both ducts are comparable, Wharton's duct is longer and has a bow-shaped course in the cranial direction.^{21,47} This results in a flow against gravity, which may facilitate stasis of submandibular saliva.^{23,25,35} Furthermore, submandibular gland saliva is more viscous than parotid gland saliva, due to a higher mucin concentration. Additionally, saliva from the submandibular gland has a higher pH, and contains twice as much calcium as parotid saliva.^{1,28,48,49} Mineralisation

is supported by accumulation of calcium and an increase in pH, which decreases the solubility of calcium phosphate in saliva. Together, these factors may favour mineralisation of a mucoid gel formed in the ductal system of a submandibular gland.^{28,50}

PREDISPOSING FACTORS

An altered saliva composition may predispose to the formation of salivary stones. It has been reported that the salivary protein content and viscosity of saliva is higher in patients with sialolithiasis than in unaffected individuals.⁵¹ Several studies showed higher calcium concentrations in saliva in patients with salivary stones than in a healthy control group.^{10,21,36,52} Saliva of patients with salivary stones also contains reduced concentrations of the crystallisation inhibitors phytate, magnesium and citrate, which may predispose to the formation of salivary stones.^{10,42} Salivary concentrations of sodium, chloride, nitrate, phosphate and sulphate did not differ from healthy individuals.

Systemic factors

Twenty-six percent of the patients with salivary stones have one or more comorbidities.³ Several studies suggested that patients with salivary stones suffer more frequently from kidney stones or stones in the gallbladder.^{17,21} However, in other studies the incidence of confirmed cholelithiasis and nephrolithiasis did not differ from the general population.^{3,25} The high prevalence of diabetes and hypertension in an Italian population with salivary stones did not correspond to other studies.^{3,17,53} Gout appears to be the only systemic disease predisposing to sialolith formation.¹ Salivary stones in gout patients are predominantly composed of uric acid.¹⁹

A decreased salivary flow rate may facilitate the formation of a salivary stone. However, there is no increased incidence of sialolithiasis in patients suffering from Sjögren's syndrome.⁴² The use of diuretics predisposes to formation of salivary stones, because diuretics decrease the salivary flow rate.⁵⁴ Twenty percent of the patients with salivary stones use diuretics, twice that of patients without salivary stones.²⁵

Smoking may decrease the antimicrobial activity of saliva, resulting in an increased bacterial load and inflammation of the salivary duct and/or gland. Huoh *et al.*²⁵ found a higher rate of smoking or history of smoking in patients with salivary stones than in the general population, although the difference did not reach statistical significance. Submandibular stones of smokers are also slightly larger (average diameter 8.7 mm) than submandibular stones of non-smokers (7.9 mm). On the other hand, the

mean age of presentation of a salivary stone is higher in smokers (50.9 years) than in non-smokers (44.9 years).²⁵

It has been suggested that residents of hard water areas are at increased risk of developing salivary calculi. However, there is no correlation between the incidence of salivary stones and the calcium content of water in different regions in England.⁵⁵

STRUCTURE

Submandibular and parotid sialoliths consist of an amorphous, mineralised core or nucleus, with concentric laminated layers or shells of organic and inorganic substances^{21,23,28,41,44,49,50,56–59} (Fig. 2). The nucleus of the sialolith has a diameter between 0.5 and 1.5 mm and a softer consistency than the peripheral parts.^{19,28} The core is usually homogeneous but may contain substructures, indicating fusion of smaller structures like sialomicrooliths.^{21,29} The concentric laminated layers are either homogenous or extremely irregular, suggesting that sialolith formation is an intermittent process.^{23,50} Scanning electron microscopy showed granular or globular, coarse structures with a diameter of 5–15 µm and pyramid structures on the surface of submandibular calculi.^{40,49,58} Hexagonal, needle-like and plate-shaped crystals on the surface of sialoliths have also been described.⁴⁶

BIOCHEMICAL COMPOSITION

Sialoliths consist of both organic and inorganic material, but there is a great variation in the relative contribution.^{42,60} The organic matrix varies in different parts of sialoliths from 23 to 100% and is mainly present in the nucleus of the sialolith and the outer shell of the sialolith.^{25,28,36} Few sialoliths are constituted of only organic material; most salivary stones contain calcium phosphates, either as hydroxyapatite or carbonate apatite.^{52,61}

The organic matrix comprises approximately 20% of the dry weight of parotid stones. Submandibular stones contain less organic material: approximately 9–12% of the dry weight.^{62,63} The organic part consists of collagen, neutral and acid glycoproteins, other proteins, lipids and carbohydrates such as glucose and mannose.^{33,60,61,63} In submandibular stones, protein contributes approximately 5% to the stone weight whereas lipids contribute 1%.^{61,63}

Proteins

In submandibular stones, protein contributes approximately 5% to the stone weight. The matrix of human submandibular stones contains higher levels of proteins than the matrix of parotid stones.⁶³ Using immunoblotting techniques, Proctor *et al.*⁶⁴

observed a large, unidentified glycoprotein in solubilised submandibular sialoliths. Lower molecular weight proteins, including statherin and acidic proline-rich protein, were also present in stones. These calcium-binding proteins are present in human submandibular saliva, and probably bind to calcium ions in sialoliths.

Amino acid analysis of the proteins in submandibular sialoliths showed relatively high levels of alanine, leucine, glutamine, aspartic acid, valine and glycine. Lysine, arginine, proline, methionine, cysteine, histidine, serine, isoleucine, phenylalanine, tyrosine and threonine were present in lower amounts.^{15,62}

Lipids

Lipids are present in the organic matrix of both submandibular and parotid stones.⁶⁵ The lipid content is not related to the weight of the stone.⁶⁶ In parotid salivary stones, these lipids mainly comprise neutral lipids (74%), glycolipids (17%) and phospholipids (9%). Of the neutral lipids, about 77% are present as free fatty acids, 14% as cholesterol and small percentages as triglycerides and cholesterol esters.⁶¹ The phospholipid composition of sialoliths is comparable to that of plasma membranes and does not resemble lipids in saliva or bacterial membranes.⁶⁶ Slomiany and co-workers^{61,63} suggested that the lipids and phospholipids are important for the initiation of the mineralisation of a salivary stone.

Inorganic matrix

Sialoliths are mainly composed of inorganic material. Submandibular stones contain between 70–80% and parotid stones around 50%.^{15,42,66,67}

The mineral component is proportional to the size of the sialolith, suggesting that mineralisation of the organic matrix increases with time.^{36,42}

Hydroxyapatite ($\text{Ca}_5(\text{PO}_4)_3\text{OH}$) is present in all submandibular stones, frequently together with whitlockite ($\text{Ca}_3(\text{PO}_4)_2$). Octacalcium phosphate ($\text{Ca}_8\text{H}_2(\text{PO}_4)_6 \cdot 5\text{H}_2\text{O}$) and brushite ($\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$) are less often identified. Whitlockite is especially found in sialoliths from Wharton's duct and often present in the nucleus. Parotid salivary stones also contain always hydroxyapatite. Whitlockite and octacalcium phosphate are more frequently present in parotid stones than in submandibular stones.^{28,45,50,64,68,69}

Minor inorganic components of sialoliths are potassium, sodium, ferrum, silicon, bromine and chloride.^{10,70} Stones retrieved from an infected gland may also contain ammonium and magnesium.⁵²

DIAGNOSIS

Most patients suspected of sialolithiasis

will present in the clinic during an acute phase of the disease. A careful anamnesis and physical examination of the patient are important. The physical examination should include bimanual palpation of the floor of the mouth in a posterior to anterior direction for submandibular glands or an intraoral palpation around Stensen's duct for parotid glands.^{1,31,48,71} The affected gland may feel firm and tender. In case of a submandibular gland, the affected side of the floor of the mouth may be elevated and inflamed.²⁶

In addition to an oral examination, several imaging techniques can be applied. Despite the relatively high percentage of inorganic material in salivary stones, between 80–95% of the submandibular stones and 43–60% of the parotid stones are radiopaque.^{1,5,17,31} Demonstration of sialoliths by radiographic examination is effective in approximately 80% of the cases⁷² (Fig. 3). The detection rates differ between intraoral occlusal radiographs and extra-oral panoramic radiographs. Extra-oral radiographs will detect fewer salivary stones because many calculi will be projected superimposed on bony structures or teeth.⁷³ This indicates that an occlusal radiograph is the most useful method for detection of a submandibular sialolith.⁷⁴ Computer tomography (CT) and cone beam computer tomography (CB-CT) can detect any size of sialolith, but have the disadvantage of a relatively high radiation dose.⁷³ Ultrasonography allows detection of stones with a diameter of 2 mm or more.^{1,4,73} This technique has the additional advantage that it also can be used during an acute episode of sialadenitis.

Radiolucent sialoliths can be imaged with sialography. A contrast agent is injected into the duct of the affected gland and subsequently radiographs are taken. Sialography is most frequently used for detection of parotid sialoliths. It is contraindicated during acute episodes of sialadenitis and in patients with an allergy to contrast media. Sialograms are up to 100% effective in detecting intraductal and intraglandular calculi.^{1,75}

Sialendoscopy is a minimally invasive technique to visualise the salivary duct system, usually performed under general anaesthesia. An endoscope with a very small diameter (0.6 mm) is introduced into the duct after the orificium has been dilated with special instruments with increasing diameters from 0.8–1.6 mm (Figs 4 and 5). The endoscope has a rinse channel that can be used to flush the duct with saline or an anti-inflammatory rinse. This flushing primarily results in a better image of the salivary ducts but may also have a therapeutic effect.^{76,77}

TREATMENT

The primary objective in the treatment of

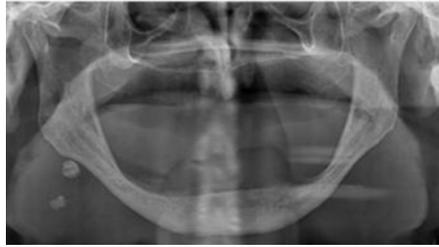


Fig. 3 Panoramic radiograph of an edentulous patient with sialoliths in the right submandibular gland (courtesy of Professor Johan Aps, University of Washington, School of Dentistry)



Fig. 4 The orificium of the parotid gland is dilated and prepared for sialendoscopy with a special probe (courtesy of Dr Erik van der Meij, department of Oral-Maxillofacial Surgery, Medical Centre Leeuwarden)

sialolithiasis should be preservation of gland function in combination with a low level of complications and discomfort for the patient.⁷⁸ Non-invasive conservative management of sialolithiasis consists of gland massage, in combination with use of sialogogues and irrigation. This treatment has the highest success rate when stones are small and located in the duct. When an infection is suspected, antibiotics should be prescribed.^{1,31,48}

Nearly all intraductal submandibular and parotid stones can be removed by a relatively simple intraoral approach under local anaesthesia^{5,31} (Fig. 6). This includes submandibular stones located near the knee of the duct.²⁴ Transoral removal is treatment of choice in patients with stones that can be palpated bimanually and/or which are localised by ultrasound within the prehilum region of the gland.^{78,79} After stone removal, it is recommended that salivary gland massage is carried out several times a day, combined with a sour diet and sialogogues to stimulate the salivary flow.⁷⁹ It is recommended to avoid use of sutures in the incised duct as this may increase the risk of scarring.^{71,73,75}

Invasive management of sialolithiasis may consist of extracorporeal shock-wave lithotripsy, sialoendoscopy or surgical removal.

Most patients experience no complaints or discomfort, but a normal functioning gland, after sialolith therapy that does not include surgical removal of the gland.^{80–82}

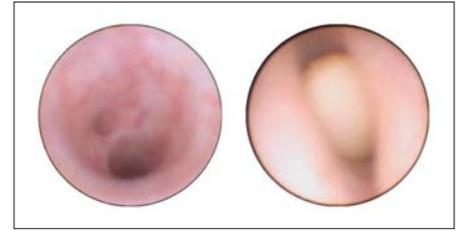


Fig. 5 Sialendoscopic images of the bifurcation of Stensen's duct (a) and a sialolith in Stensen's duct (b) (courtesy of Dr Erik van der Meij, department of Oral-Maxillofacial Surgery, Medical Centre Leeuwarden)



Fig. 6 Transoral removal of a submandibular sialolith after a surgical incision of 5 mm has been made in the orificium of Wharton's duct (courtesy of Professor Johan Aps, University of Washington, School of Dentistry)

After transoral surgical removal of submandibular stones, the secretion rate of the treated gland is in 75% of the cases similar to that of the contralateral gland.²⁴ Recovery of function of the salivary gland is related to factors such as glandular infection, the diameter of the sialolith and the age of the patients. Patients with normal salivary secretion from a submandibular gland after transoral removal of a sialolith were significantly younger than those patients in which saliva secretion from the treated gland was decreased compared to the contralateral unaffected submandibular gland. The duration of symptoms before treatment was not related to recovery.^{11,24,83}

Recurrence of sialoliths is rather uncommon, and is estimated to occur in 1–10% of the patients.^{17,72,78,79,84}

1. Williams M F. Sialolithiasis. *Otolaryngol Clin North Am* 1999; **32**: 819–834.
2. Levy D M, Remine W H, Devine K D. Salivary gland calculi. Pain, swelling associated with eating. *J Am Med Assoc* 1962; **181**: 1115–1119.
3. Zenk J, Constantinidis J, Kydles S, Hornung J, Iro H. Klinische und diagnostische Befunde bei der Sialolithiasis. *HNO* 1999; **47**: 963–969.
4. Zenk J, Koch M, Klintworth N *et al*. Sialoendoscopy in the diagnosis and treatment of sialolithiasis: a study on more than 1000 patients. *Otolaryngol Head Neck Surg* 2012; **147**: 858–863.
5. McGurk M, Escudier M P, Brown J E. Modern management of salivary calculi. *Br J Surg* 2005; **92**: 107–112.

6. Pace C, Ward S. Incidental finding of sialolithiasis in the sublingual gland: a diagnostic dilemma. *Dent Update* 2011; **38**: 704–705.
7. McGurk M, Escudier M P, Brown E. Modern management of obstructive salivary gland disease. *Ann R Australas Coll Dent Surg* 2004; **17**: 45–50.
8. Taher A A. The incidence and composition of salivary stones (sialolithiasis) in Iran: analysis of 95 cases – a short report. *Singapore Dent J* 1989; **14**: 33–35.
9. Esser R J, Zecha J J. Submandibulaire speekselstenen. *Ned Tijdschr Geneesk* 1976; **120**: 817–821.
10. Su Y X, Zhang K, Ke Z, Zheng G, Chu M, Liao G. Increased calcium and decreased magnesium and citrate concentrations of submandibular/sublingual saliva in sialolithiasis. *Arch Oral Biol* 2010; **55**: 15–20.
11. Nishi M, Mimura T, Marutani K, Noikura T. Evaluation of submandibular gland function by sialo-scintigraphy following sialolithectomy. *J Oral Maxillofac Surg* 1987; **45**: 567–571.
12. Anneroth G, Hansen L S. Minor salivary gland calculi: a clinical and histopathological study of forty-nine cases. *Int J Oral Surg* 1983; **12**: 80–89.
13. Yamamoto H, Sakae T, Takagi M, Otake S, Hirai G. Weddelite in submandibular gland calculus. *J Dent Res* 1983; **62**: 16–19.
14. Marchal F, Kurt A M, Dulguerov P, Lehmann W. Retrograde theory in sialolithiasis formation. *Arch Otolaryngol Head Neck Surg* 2001; **127**: 66–68.
15. Harrill J A, King J S, Boyce W H. Structure and composition of salivary calculi. *Laryngoscope* 1959; **59**: 481–492.
16. Escudier M P, McGurk M. Symptomatic sialadenitis and sialolithiasis in the English population, an estimate of the cost of hospital treatment. *Br Dent J* 1999; **186**: 463–466.
17. 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**: 135–138.
18. Gupta A, Rattan D, Gupta R. Giant sialoliths of submandibular duct: report of two cases with unusual shape. *Contemp Clin Dent* 2013; **4**: 78–80.
19. Blatt I M, Denning R M, Zumbege J H, Maxwell J H. Studies in sialolithiasis. I. The structure and mineralogical composition of salivary gland calculi. *Ann Otol Rhinol Laryngol* 1958; **67**: 595–617.
20. Rauch S, Gorlin R J. Diseases of the salivary glands. *Oral pathology* 1970; 962.
21. Harrison J D. Causes, natural history, and incidence of salivary stones and obstructions. *Otolaryngol Clin N Am* 2009; **42**: 927–947.
22. Bullock K N. Parotid and submandibular duct calculi in three successive generations of one family. *Postgrad Med J* 1982; **58**: 35–36.
23. Hiraide F, Nomura Y. The fine surface structure and composition of salivary calculi. *Laryngoscope* 1980; **90**: 152–158.
24. Van den Akker H P, Busemann-Sokole E. Submandibular gland function following transoral sialolithectomy. *Oral Surg Oral Med Oral Pathol* 1983; **56**: 351–356.
25. Huoh K C, Eisele D W. Etiologic factors in sialolithiasis. *Otolaryngol Head Neck Surg* 2011; **145**: 935–939.
26. Seldin H M, Seldin D, Rakower W. Conservative surgery for the removal of salivary calculi. *Oral Surg Oral Med Oral Pathol* 1953; **6**: 579–587.
27. Pullon P A, Miller A S. Sialolithiasis of accessory salivary glands: review of fifty-five cases. *J Oral Surg* 1972; **30**: 832–834.
28. Teymoortash A, Buck P, Jepsen H, Werner J A. Sialolith crystals localized intraglandularly and in the Wharton's duct of the human submandibular gland: an X-ray diffraction analysis. *Arch Oral Biol* 2003; **48**: 233–236.
29. Jensen J L, Howell F V, Rick G M, Corneal R W. Minor salivary gland calculi. *Oral Surg Oral Med Oral Pathol* 1979; **47**: 44–50.
30. Yamane G M, Scharlock S E, Jain R, Sundaraj M, Chaudry A P. Intra-oral minor salivary gland sialolithiasis. *J Oral Med* 1984; **39**: 85–90.
31. Siddiqui S J. Sialolithiasis: an unusually large submandibular salivary stone. *Br Dent J* 2002; **193**: 89–91.
32. Epivatianos A, Harrison J D, Dimitriou T. Ultrastructural and histochemical observations on microcalculi in chronic submandibular sialoadenitis. *Oral Pathol* 1987; **16**: 514–517.
33. Epivatianos A, Harrison J D. The presence of microcalculi in normal human submandibular and parotid salivary glands. *Arch Oral Biol* 1989; **34**: 261–265.
34. Harrison J D, Epivatianos A, Bhatia S N. Role of microliths in the aetiology of chronic submandibular sialadenitis: a clinicopathological investigation of 154 cases. *Histopathology* 1997; **31**: 237–251.
35. Bodner L. Parotid sialolithiasis. *J Laryngol Otol* 1999; **113**: 266–267.
36. Harrison J D. Histology and pathology of sialolithiasis. *Salivary gland diseases New York, USA, Thieme, 2005*: 71–78.
37. Mimura M, Tanaka N, Ichinose S, Kimijima Y, Amagasa T. Possible etiology of calculi formation in salivary glands: biophysical analysis of calculus. *Med Mol Morphol* 2005; **38**: 189–195.
38. Triantafyllou A, Harrison J D, Garrett J R. Microliths in the parotid of ferret investigated by electron microscopy and microanalysis. *Int J Exp Path* 2009; **90**: 439–447.
39. Anneroth G, Eneroth C M, Isacsson G. Crystalline structure of salivary calculi. A microradiographic and microdiffraction study. *J Oral Pathol* 1975; **4**: 266–272.
40. Lustmann J, Shteyer A. Salivary calculi: ultrastructural morphology and bacterial etiology. *J Dent Res* 1981; **60**: 1386–1395.
41. Isacsson G, Hammarström L. An enzyme histochemical study of human salivary duct calculi. *J Oral Pathol* 1983; **12**: 217–222.
42. Proctor G B, Osailan S M, McGurk M, Harrison J D. Sialolithiasis – pathophysiology, epidemiology and aetiology. In Nahlieli O (ed) *Modern management of preserving the salivary glands*. pp 91–142. Israel: Isradon Publishing House, 2007.
43. Anneroth G, Eneroth C M, Isacsson G, Lundquist P G. Ultrastructure of salivary calculi. *Scand J Dent Res* 1978; **86**: 182–192.
44. Teymoortash A, Wollstein A C, Lippert B M, Peldszus R, Werner J A. Bacteria and pathogenesis of human salivary calculus. *Acta Otolaryngol* 2002; **122**: 210–214.
45. Marchal F, Dulguerov P. Sialolithiasis management – the state of the art. *Arch Otolaryngol Head Neck Surg* 2003; **129**: 951–956.
46. Kasaboglu O, Nuray E, Tümer C, Akkocaoglu M. Micromorphology of sialoliths in submandibular salivary gland: a scanning electron microscope and X-ray diffraction analysis. *J Oral Maxillofac Surg* 2004; **62**: 1253–1258.
47. Zenk J, Hosemann W G, Iro H. Diameters of the main excretory ducts of the adult human submandibular and parotid gland: a histologic study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; **85**: 576–580.
48. Pollack C V, Severance H W. Sialolithiasis: case studies and review. *J Emergency Med* 1990; **8**: 561–565.
49. Tanaka N, Ichinose S, Adachi Y, Mimura M, Kimijima Y. Ultrastructural analysis of salivary calculus in combination with X-ray microanalysis. *Med Electron Microsc* 2003; **36**: 120–126.
50. Anneroth G, Eneroth C M, Isacsson G. Morphology of salivary calculi. The distribution of the inorganic component. *J Oral Pathol* 1975; **4**: 257–265.
51. Afanas'ev V V, Tkalenko A F, Abdusalomov M R. Analysis of salivary pool composition in patients with different results of sialolithiasis treatment by sialolithiopsy. *Stomatologia* 2003; **82**: 36–38.
52. Grases F, Santiago C, Simonet B M, Costa-Bauza A. Sialolithiasis: mechanism of calculi formation and etiologic factors. *Clin Chim Acta* 2003; **334**: 131–136.
53. Laforgia P D, Favia G F, Chiaravalle N, Lacaíta M G, Laforgia A. Clinico-statistical, morphologic and microstructural analysis of 400 cases of sialolithiasis. *Minerva Stomatol* 1989; **38**: 1329–1336.
54. Nederfors T, Nauntofte B, Twetman S. Effects of furosemide and bendroflumethiazide on saliva flow rate and composition. *Arch Oral Biol* 2004; **49**: 507–513.
55. Sherman J A, McGurk M. Lack of correlation between water hardness and salivary calculi in England. *Br J Oral Maxillofac Surg* 2000; **38**: 50–53.
56. Perrotta R J, Williams J R, Selve R W. Simultaneous bilateral parotid and submandibular gland calculi. *Arch Otolaryngol Head Neck Surg* 1978; **104**: 469–470.
57. Vignoles M, Faure J, Legros R, Bonel G, Guichard M. Identification of the mineral constituents of various salivary calculi by study of their thermal behavior. *J Biol Buccale* 1980; **8**: 103–115.
58. Yamamoto H, Sakae T, Takagi M, Otake S. Scanning electron microscopic and X-ray microdiffraction studies on sialolith-crystals in human submandibular glands. *Acta Pathol Jpn* 1984; **34**: 47–53.
59. Kodaka T, Debari K, Sano T, Yamada M. Scanning electron microscopy and energy-dispersive X-ray microanalysis studies of several human calculi containing calcium phosphate crystals. *Scanning Microsc* 1994; **8**: 241–256.
60. Jayasree R S, Gupta A K, Vivek V, Nayar V U. Spectroscopic and thermal analysis of a submandibular sialolith of Wharton's duct resected using Nd: YAG laser. *Lasers Med Sci* 2008; **23**: 125–131.
61. Slomiany B L, Murty V L N, Aono M, Slomiany A, Mandel I D. Lipid composition of the matrix of human submandibular salivary gland stones. *Arch Oral Biol* 1982; **27**: 673–677.
62. Osuoji C I, Rowles S L. Studies on the organic composition of dental calculus and related calculi. *Calcif Tissue Res* 1974; **16**: 193–200.
63. Slomiany B L, Murty V L N, Aono M, Slomiany A, Mandel I D. Lipid composition of human parotid salivary gland stones. *J Dent Res* 1983; **62**: 866–869.
64. Proctor G B, McGurk M, Harrison J D. Protein composition of submandibular stones. *J Dent Res* 2005; **84**(Suppl): Ab0218.
65. Mandel I D, Eisenstein A. Lipids in human salivary secretions and salivary calculus. *Arch Oral Biol* 1969; **14**: 231–233.
66. Boskey A L, Boyan–Salyers B D, Burstein L S, Mandel I D. Lipids associated with mineralization of human submandibular gland sialoliths. *Arch Oral Biol* 1981; **26**: 779–785.
67. Ekberg O, Isacsson G. Chemical analysis of the inorganic component of human salivary duct calculi. *Arch Oral Biol* 1981; **26**: 951–953.
68. Hohling H J, Schöpfer H. Morphological investigations of apatite nucleation in hard tissue and salivary stone formation. *Naturwissenschaften* 1968; **55**: 545.
69. Burstein L S, Boskey A L, Tannenbaum P J, Posner A S, Mandel I D. The crystal chemistry of submandibular and parotid salivary gland stones. *J Oral Pathol* 1979; **8**: 284–291.
70. Szalma J, Böddi K, Lempel E *et al*. Structural analysis and protein identification from submandibular salivary stones. *J Dent Res* 2011; A391.
71. Whinery J. Salivary calculi. *J Oral Surg* 1954; **12**: 43–47.
72. Ellies M, Laskawi R, Arglebe C, Schott A. Surgical management of nonneoplastic diseases of the submandibular gland. A follow-up study. *Int J Oral Maxillofac Surg* 1996; **25**: 285–289.
73. Bodner L. Salivary gland calculi: diagnostic imaging and surgical management. *Comp Contin Educ Dent* 1993; **14**: 572–584.
74. Baurmash H D. Submandibular salivary stones: current management modalities. *J Oral Maxillofac Surg* 2004; **62**: 369–378.
75. McKenna J P, Bostock D J, McMenamin P G. Sialolithiasis. *Am Fam Physician* 1987; **36**: 119–125.
76. Bowen M A, Tauzin M, Kluka E A, Nuss D W, DiLeo M, McWhorter A J, Schaitkin B, Walvekar R R. Diagnostic and interventional sialendoscopy: a preliminary experience. *Laryngoscope* 2011; **121**: 299–303.
77. Strychowski J E, Sommer D D, Gupta M K, Cohen N, Nahlieli O. Sialendoscopy for the management of obstructive salivary gland disease: a systematic review and meta-analysis. *Arch Otolaryngol Head Neck Surg* 2012; **138**: 541–547.
78. Zenk J, Constantiniadis J, Al-Kadab B, Iro H. Transoral removal of submandibular stones. *Arch Otolaryngol Head Neck Surg* 2001; **127**: 432–436.
79. Zenk J, Gottwald F, Bozzato A, Iro H. Speichelsteine der Glandula submandibularis. Setinentfernung mit Organerhalt. *HNO* 2005; **53**: 243–249.

80. Isacson G, Ahlner B, Lundquist PG. Chronic sialadenitis of the submandibular gland. A retrospective study of 108 cases. *Arch Otorhinolaryngol* 1981; **232**: 91–100.
81. Yoshimura Y, Morishita T, Sugihara T. Salivary gland function after sialolithiasis: scintigraphic examination of submandibular glands with ^{99m}Tc -pertechnetate. *J Oral Maxillofac Surg* 1989; **47**: 704–710.
82. Makdissi J, Escudier MP, Brown JE, Osailan S, Drage N, McGurk M. Glandular function after intraoral removal of salivary calculi from the hilum of the submandibular gland. *Br J Oral Maxillofac Surg* 2004; **42**: 538–541.
83. Zenk J, Koch M, Mantsopoulos K, Klintworth N, Schapfer M, Iro H. Der Stellenwert der extrakorporalen Stosswellen-lithotripsie bei der Therapie der Sialolithiasis. *HNO* 2013; **61**: 306–311.
84. Nahlieli O, Baruchin A M. Long-term experience with endoscopic diagnosis and treatment of salivary gland inflammatory diseases. *Laryngoscope* 2000; **110**: 988–993.