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Original Article

Detecting calcified pulp stones in patients with periodontal diseases using digital panoramic and periapical radiographies

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KEYWORDS
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Periodontally involved teeth

Background/purpose: Pulp stones are discrete calcified masses appearing in the dental pulp of healthy, disease and unerupted teeth. They are presented freely within the pulp tissue or attached and embedded in any part of coronal and radicular dentin. Here, the purposes of this study were to identify the presence of pulp stones in periodontal patients using digital panoramic and periapical radiographies, and to determine the association with gender, age, tooth type and dental arch.

Materials and methods: This is a retrospective study on selected records of 465 dental samples obtained between January and December, 2020. Data were collected from patients diagnosed with generalized chronic periodontitis and accepted the full periodontal treatment covered by the Government's Periodontal Health Care Program. Their digital panoramic (DPR) examination and full mouth periapical radiographic (DPA) examination (including 12 periapical and 4 bitewing images) were performed at the Outpatient Clinics of the Department of Stomatology, Taichung Veterans General Hospital. Patients were segregated into various groups according to their age, gender and tooth locations. All radiographic images were examined by a dental radiologist and two dentists to identify the presence of pulp stone calcifications and their associated factors using the Sirona applications software. Records were analyzed using SPSS version 22.0 based on tests of Pearson Chi-square and McNemar correlation.

Results: From 271 males and 194 females, a total of 465 DPR and 7440 DPA radiographs were studied. Pulp stone calcifications were identified in 270 (58.0%) subjects in DPR images and 348 (74.8%) subjects in DPA images (for 1 or more teeth per subject). We detected calcified opacities in 1031 teeth with DPR images and in 1326 teeth with DPA images from a total of 12,407 teeth. The incidence of pulp stones was similar across genders, but different in tooth locations and dental arch sextant. Moreover, pulp stones were detected more often on maxillary molars

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and subjects of old ages (>40 years). Digital panoramic and periapical radiography showed significant differences in the detection of pulp stone calcifications ($P < 0.05$), and detected better with digital periapical radiography examination.
Conclusion: We found 58.0% (n = 645) of our patients with pulp stones using digital panoramic radiography, and 74.8% using digital periapical radiography. Regarding individual teeth, only 8.5% of pulp stones were observed in digital panoramic radiography and 10.6% in digital periapical radiography. Pulp stones were more often seen in maxillary molar teeth and old patients of ages >40 years old using periapical radiography examination especially in those patients with periodontally condition. As a two-dimensional imaging system, digital periapical radiography is recommended for a definitive and routine assessment in patients suspected of hard tissue abnormality and pulp calcification formation.

Introduction

Pulpal calcified structures are fairly common. Such calcification of dental pulp tissue, often known as denticle, pulp stone, or dystrophic calcification, has been studied for over a decade. Pulp stones may occur in any one or multiple teeth, deciduous or permanent, healthy or disease, and even in unerupted or impacted teeth.[1,2] Pulp stone calcifications vary in number from one or more in a single tooth or in multiple teeth. Their size varies from minute particles to large calcified mass, occluding a part or the entire pulp cavity. Pulp stones are more often seen in coronal pulp although they are also found in radicular areas.[3–5] These calcifications and/or stones are usually asymptomatic, except when impinging on the nerve or blood vessel.[6] (see Figs. 1 and 2)

Despite a number of microscopic and histochemical studies, the exact causes of pulp calcification remains largely unclear.[7,8] A host of factors like age, dental trauma, periodontal disease, orthodontic treatment and systemic disease are implicated.[7,9–16] The prevalence of pulp stones ranges from 8% to 90%.[5,6,17–19] The detection of pulpal calcifications in human dental pulp, based on radiographic examinations, has been reported to be 2.1%—63.6% across different populations.[17,20] The occurrence of pulp calcifications are generally believed to be under-estimated. That is mainly because small calcified masses (<200 um) are not easily detected with radiographic imaging.[2] The current digital imaging systems, including periapical, panoramic and cone-beam computed tomography radiography can provide more realistic and accurate images.[17,20–22] Hence, visualizing the orientation and dimensions of pulpal structures can be better in replicating and measuring the pulp stone calcifications. However, no such related investigation has been reported regarding two commonly used clinical radiographic techniques on diagnosing pulp tissue disease and occurrence of pulp stone calcifications.

The purpose of this study was: (a) to compare two commonly used digital radiographic techniques, i.e., panoramic and periapical radiograhy, in detecting pulp stone calcifications at dental pulps of patients with periodontal diseases; (b) to determine the association between

Figure 1 Digital Panoramic radiography is a commonly used clinical tool to quantify the pulpal radiopacities or calcifications (red circle).

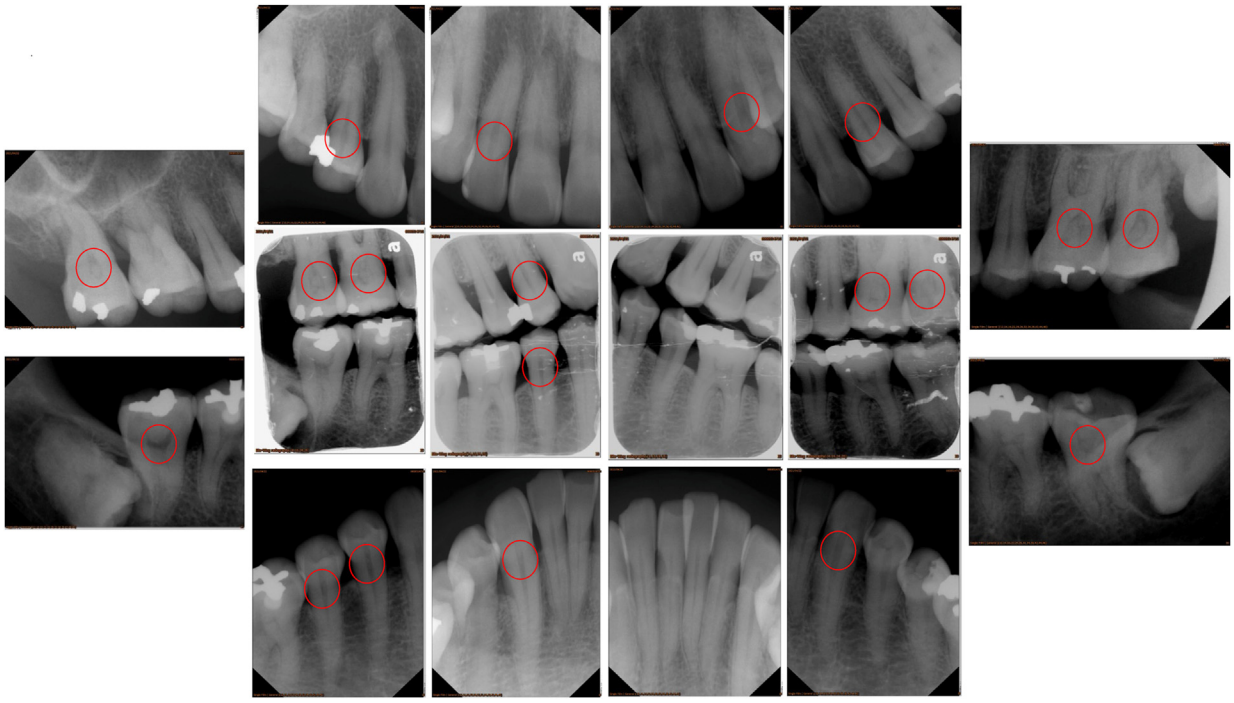

Figure 2 Digital periapical radiography of the same patient (Fig. 1) showed more than one pulpal radiopacities or calcifications (red circle).

the occurrence of pulpal calcifications and related factors like age, gender, tooth type and dental arch sextant.

Materials and methods

Patient selection

Our study protocol was approved by the Institutional Review Board of Research Ethics Committee of Taichung Veterans General Hospital, Taiwan, and complied with guidelines in the Declaration of Helsinki. We retrospectively reviewed and evaluated the radiological records of a total of 465 patients (271 male, 194 female), including 12,407 teeth (7229 male, 5178 female). Patients all received full mouth periodontal treatment under the diagnosis of chronic generalized periodontitis, requiring radiographic examination as part of their oral examination and treatment modality. Periodontal treatment was covered by the Government's Periodontal Health Care Program. Images were taken with digital panoramic radiography (DPR) and full mouth periapical radiography (PAR) (including 12 periapical and 4 bitewing images). Procedures were taken at the Outpatient Clinics of the Department of Stomatology, Taichung Veterans General Hospital between January and December of 2020, before the treatment planning setting. Patients were divided into various groups according to their age, gender and tooth locations. Patients aged between 17 and 99 years old.

Image taking and data record

Radiographic examinations were taken using a digital radiograhy system (Sirona, Orthophos XG, Bensheim, Germany) under the manufacturer's recommended exposure settings (8 MA, 69Kvp and 14 s). X-ray images were displayed directly on a 4G monitor at a resolution of 2560 $\times$ 1600 pixels. Images measurements were performed with the manufacturer's software (EBM dental, Taichung, Taiwan). Image contrast and brightness were adjusted using the image-processing tool for optimal visualization. Teeth were scored as having a pulp stone when a definitive radiopaque mass had been observed in the pulp space. The pulp stone was evaluated and identified from both the DPR and PAR images, and confirmed by a senior dental radiologist and two endodontists of our hospital. Intra- or inter-observer variability was determined at the level of $<$5%.

Statistical analyses

Data were analyzed using the standard statistical software (IBM SPSS version 22.0, New York, USA). Bivariate associations between genders and comparisons of the DPR and the PAR imaging modalities in terms of pulp stone identifications were evaluated using Pearson's Chi-square test. McNemar correlations test was used to determine the relationship with age, tooth location and dental arches sextants. All statistical analyse were done using SPSS version 22.0 (IBM corporation, Armonk, NY, USA) with a significance P level set at $<$0.05.

Results

A total of 465 patients (194 females, 271 males) were included in this one year retrospective study. Their mean of age was 48.2 $\pm$ 17.7 years (ranged from 17 to 99 years). The tooth missing rate was 16.5% (1030/6208) for females,

and 16.6% (1443/8672) for males (Table 1). Pulp cavity radiopacities were detected in 270 (58.0%) subjects on DPR images and 348 (74.8%) subjects on DPA images in 1 or more teeth, which included 110 (23.6%) in female and 160 (34.4%) in male on DPR images, and 146 (31.3%) in female and 202 (43.4%) in male on DPA images. Of individual teeth, the occurrence of pulp stone calcifications was observed 1031 teeth on the DPR images, and 1326 teeth on the DPA images (Table 1). In those DPR images, 56 patients (20.7%) had only one tooth with pulp chamber calcification, while 207 patients (76.6%) had pulp stone in more than one tooth, and 7 (2.5%) patients had more than 10 teeth. In the DPA images, 64 patients (18.3%) had only one tooth with pulp chamber calcification, while 274 patients (78.7%) had more than one tooth and 10 patients (2.8%) had more than 10 teeth with pulp chamber calcification. Regarding the location and root number of teeth, pulp stones in one, two and three root teeth were found respectively in 11.44% (118/1031), 23.37% (241/1031) and 65.17% (672/1031) on DPR images. From observation of DPA images, pulp stones in one, two, three root teeth were identified respectively in 22.47% (298/1326), 33.1% (439/1326), and 44.41% (589/1326) of images (Table 1). Comparisons of pulp stones between genders and across ages and/or canals were shown in Table 1. The detection of pulp stones was not significantly different across genders nor for age groups of <20 and of 21—40 years. More prevalent and obviously pulp stones were identified in the age groups of 41—60 years, and of >60 years (Table 1). Table 2 summarizes the distribution of teeth with or without pulp stones formation according to tooth location, type of tooth and dental arch sextants. The prevalence of pulp stones in the maxillary and mandibular arches was about equal in DPA images, but found more often in the DPR images at the maxillary area. So forth, pulp stones were more prevalent in the maxillary arch (10.4%) than in the mandibular arch (6.1%) in DPR images, with a significant difference between arches (Table 2). Moreover, calcified mass in the right and left side were equally observed. Calcify pulp stones were clearly observed in the maxillary molar region, and also more often with old ages especially in periodontally involved teeth. Finally, the occurrence of pulp stones was the highest at the maxillary first molar (22.1% in DPR vs 28.7% in DPA), followed by the maxillary second molar (24.9% in DPR vs 19.6% in DPA), and mandibular first molar (15.6% in DPR vs 17.2% in DPA) ($P < 0.05$). The mandibular incisors were the least affected teeth (0.3% in DPR vs 2.4% in DPA) (Table 2). Overall, 8.3% (1031/12407) of teeth had pulp stones as examined by DPR examination, whereas 10.6% of the teeth (1326/12407) had a pulp stone easily detected in DPA images. We suggested that digital periapical radiography examinations are a great opportunity to observe and identify pulpal calcification prior aggressive dental procedures to be scheduled (Table 1).

Discussion

Pulpal calcifications occur widely in dental pulps of healthy or diseased humans, and even in un-erupted or impacted

Table 1 Distribution of examined teeth with pulp stone calcification by patient's characteristics.

465 subjects (n = 14880 teeth)			Full Mouth												
			Missing tooth					Pulp stone identified							
			Yes		No		*p* value	Panoramic				Periapical			*p* value
								Yes		No		Yes		No	
	n	(%)	n	(%)	n	(%)		n	(%)	n	(%)	n	(%)	n	(%)	
Gender							0.956								0.024
Female	194	41.7	183	39.4	11	2.4		110	23.6	84	18.1	146	31.3	46	9.8	
	6208		1030	7.0	5178	34.7		448	3.7	4730	38.1	587	4.7	4591	37.0	
Male	271	58.2	258	55.4	13	2.7		160	34.4	111	23.8	202	43.5	71	15.3	
	8672		1443	9.6	7229	48.5		583	4.6	6646	53.5	739	5.9	6490	52.3	
Subjects	465		441	94.8	24	5.1		270	58.0	195	41.9	348	74.8	117	25.1	
Teeth no	14880		2473	16.6	12407	83.3		1031	8.3	11376	91.6	1326	10.6	11081	89.3	
Age							<0.001**								0.006**
17—20	96	0.6	6	0.2	90	0.7		6	0.5	84	0.7	6	0.4	84	0.7	
21—40	1664	11.1	216	8.7	1448	11.6		90	8.7	1358	11.9	128	9.6	1320	11.9	
41—60	8288	55.6	1291	52.2	6997	56.3		630	61.1	6367	55.9	777	58.5	6220	56.1	
>60	4832	32.4	960	38.8	3872	34.2		305	29.5	3567	31.3	415	31.2	3457	31.1	
n =	14880		2473		12407			1031		11376		1326		11081		
Root							<0.001**								<0.001**
1 canal	5580	37.5	217	8.7	5363	43.2		118	11.4	5245	46.1	298	22.4	4774	43.0	
2 canals	3720	25.0	260	10.5	3460	27.8		241	23.3	3219	28.2	439	33.1	3021	27.2	
3 canals	5580	37.5	1996	80.7	3584	28.8		672	65.1	2912	25.5	589	44.4	3286	29.4	
n =	14880		2473		12407			1031		11376		1326		11081		

Chi—Square test. *$p < 0.05$ significantly difference, **$p < 0.01$ more significantly difference.

Table 2 Distribution of examined teeth with pulp stone calcification by teeth characteristics in different location.

Pulp stone	Full Mouth					Maxillary					Mandibular					Left					Right				
	Panoramic		Periapical		*p* value	Panoramic		Periapical		*p* value	Panoramic		Periapical		*p* value	Panoramic		Periapical		*p* value	Panoramic		Periapical		*p* value
	n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)	
Overall					<0.001**					0.107					<0.001**					<0.001**					<0.001**
No	11376	91.6	11081	89.3		5497	89.2	5458	88.7		5879	93.8	5623	89.7		5639	91.3	5493	88.9		5737	92.0	5588	89.6	
Yes	1031	8.3	1326	10.6		644	10.4	683	11.1		387	6.1	643	10.2		536	8.6	682	11.0		495	7.9	644	10.3	
3rd molar					<0.001**					<0.001**					0.065					0.013*					<0.001**
No	617	93.0	644	97.1		255	89.4	275	96.4		362	95.7	369	97.6		301	92.9	311	95.9		316	93.2	333	98.2	
Yes	46	6.9	19	2.8		30	10.5	10	3.5		16	4.2	9	2.3		23	7.0	13	4.0		23	6.7	6	1.8	
2 nd molar					0.002**					<0.001**					1.000					0.012*					0.090
No	1198	81.4	1238	84.2		565	75.0	605	80.3		633	88.2	633	88.4		588	79.8	611	83.0		610	83.1	627	85.4	
Yes	272	18.5	232	15.7		188	24.9	148	19.6		84	11.7	84	11.7		148	20.1	125	16.9		124	16.8	107	14.5	
1st molar					0.312					0.032*					0.326					0.852					0.242
No	1098	75.6	1114	76.7		520	67.8	546	71.2		578	84.2	568	82.7		517	73.4	520	73.8		581	77.6	594	79.4	
Yes	354	24.3	338	23.2		246	22.1	220	28.7		108	15.6	118	17.2		187	26.5	184	26.1		167	22.3	154	20.5	
2nd premolar					<0.001**					0.003**					<0.001**					<0.001**					<0.001**
No	1547	91.0	1456	85.6		772	92.0	743	88.5		775	90.1	713	82.9		773	90.9	733	86.2		774	91.1	723	85.1	
Yes	152	8.9	243	14.3		67	7.9	96	11.4		85	9.8	147	17.0		77	9.0	117	13.7		75	8.8	126	14.8	
1st premolar					<0.001**					0.003**					<0.001**					<0.001**					<0.001**
No	1671	94.9	1564	(88.8		825	96.0	801	93.2		846	93.8	763	84.6		840	95.5	785	89.3		831	94.3	779	88.4	
Yes	89	5.0	196	11.1		34	3.9	58	6.7		55	5.9	138	15.3		39	4.4	94	10.6		50	5.6	102	11.5	
Canine					<0.001**					<0.001**					<0.001**					<0.001**					<0.001**
No	1766	96.7	1686	(92.3		874	96.7	849	94.0		892	96.6	837	90.6		881	96.8	833	91.5		885	96.6	853	93.1	
Yes	60	3.2	140	7.6		29	3.2	54	5.9		31	3.3	86	9.3		29	3.1	77	8.4		31	3.3	63	6.8	
Lateralincisor					<0.001**					0.037*					<0.001**					0.015*					<0.001**
No	1747	98.0	1698	(95.2		845	96.5	830	94.8		902	99.4	868	95.7		873	97.7	857	95.9		874	98.3	841	94.6	
Yes	35	(1.9	84	4.7		30	3.4	45	5.1		5	0.5	39	4.2		20	2.2	36	4.0		15	1.6	48	5.3	
Centralincisor					<0.001**					<0.001**					<0.001**					<0.001**					<0.001**
No	1732	98.6	1681	95.7		841	97.6	809	94.0		891	99.6	872	97.5		866	98.5	843	95.9		866	98.8	838	95.6	
Yes	23	1.3	74	4.2		20	2.3	52	5.9		3	0.3	22	2.4		13	1.4	36	4.0		10	1.1	38	4.3	

McNemar test. *$p < 0.05$ significantly difference, **$p < 0.01$ more significantly difference.

Table 3 Previous reports on the prevalence of pulp stone calcifications in different populations.

Authors	Population	Study Model	Samples		Pulp stone (%)		Remark
			Subject	Teeth	Subject	Teeth	
Hamasha et al.[27] (1998)	Jordanian	Periapical/Bitewing	814	4573	51.4	22.4	Molar
Ranjitkar et al.[42] (2002)	Australians	Bitewing	217	3296	46.1	10.1	Max molar
Gulsahi et al.[28] (2009)	Turkish	Periapical	519	13474	12.0	5.0	Molar
Sener et al.[18] (2009)	Turkish	Periapical/Bitewing	536	15326	38.0	4.8	
AlNazhan[43] (2011)	Saudi Arabia	Bitewing	600	8456	—	10.2	
Al-Ghurabi[26] (2012)	Iraqi	Panoramic	390	3758	34.8	7.0	Molar
Colak et al.[40] (2012)	Turkish	Bitewing	814	8600	63.6	27.8	Max molar
Sisman et al.[41] (2012)	Turkish	Bitewing	469	6926	57.6	15.0	Max molar
Turkal et al.[29] (2013)	Turkish	Panoramic	6912	96240	12.7	2.1	Max
Kannan et al.[30] (2015)	Malaysian	Periapical	361	1779	44.9	15.7	Molar
Kumar et al.[33] (2015)	India	Periapical	240	6939	55.0	—	
Jayam et al.[31] (2017)	Nepal	Panoramic	1000	32000	51.4	9.4	Max molar
Kalaji et al.[36] (2017)	Yemini	Panoramic	913	8802	18.6	3.9	Max
Hassanabadi et al.[34] (2018)	Iranian	Panoramic	493	3235	15.2	5.3	
Kuzekanani et al.[35] (2018)	Iranian	Periapical	412	800	31.5	9.6	Max molar
Sandhu et al.[32] (2018)	Indian	Periapical	500	4625	26.0	18.0	Max molar
Yousuf et al.[44] (2018)	South Indian	Panoramic	374	—	14.4	—	Max
Alawjali[38] (2019)	Libyan	Panoramic	1200	16738	30.2	8.4	Max
Sadoon et al.[37] (2019)	Saudi Arabia	Periapical	298	1306	28.0	12.0	Molar
SriVarsha[19] (2019)	Chennai	Panoramic	100	3020	58.0	5.0	Max molar
Chen et al. (present study)	Taiwanese	Panoramic	465	12407	58.0	8.3	Max molar
		Periapical			74.8	10.6	

teeth. Calcified masses in the pulps have been studied for many years.[2,5,13] The consensus is the occurrence of such calcification mostly is due to dystrophy or degeneration of dental pulp tissues. Therefore, dystrophic calcification is a physiological and/or pathological manifestation.[1] The occurrence of pulp stones is known to be related to functional disturbance due to aging, tooth trauma, periodontal disease, pathologic changes in enamel or dentin structures, and systemic diseases such coronary artery disease, diabetes mellitus and renal dysfunction.[7–13,15,19,23–25]

The prevalence of pulpal calcification varies from 8% to 90%.[5,6,17–19,26] The variations may be due to differences in measuring tools and study populations. It is also believed that calcifications with diameter <200 um are not readily identifiable on radiographic images.[5,13,17] Based on radiographic examinations in the past 20 years, the occurrence of pulp stones are reported to be 2.1%–63.6% in different populations and geographical locations: e.g., Hamasha et al. on Jordanian; Gulsahi et al. and Turkal et al. on Turkish; Al-Ghurabi & Najm on Iraqi; Kannan et al. on Malaysian; Kumar et al. and Sandhu et al. on Indian; Jayam et al. on Nepalese; Hassanabadi et al. and Kuzekanani et al. on Iranian; Kalaji et al. on Yemini; Sadoon et al. on Saudi Arabia and Alawjaki on Libyan (Table 3).[26–38] Digital panoramic radiography and periapical radiography are currently the most widely used clinical tools in intraoral examinations. They are typically used to calibrate the bony defect and abnormal radioluceny and radiopacity shadow in the oral cavity. Newly developed CBCT provides a reliable visualization of the orientation and dimensions of oral structures.[20–22,39] But digital panoramic and periapical radiography can provide realistic images allowing different angulations, and the ease in replicating measurements. Results of our present study comply with previous reports, utilizing DPR and DPA images to identify and characterize pulp cavity opacities.

The prevalence of pulp stone calcifications we found in this present study is 58% of personal subjects (270/465) in DPR images and 74.8% (348/465) in DPA images. Such findings are similar to those reported earlier by Colak et al. (2012), Sisman et al. (2012), Kumar et al. (2015), and SriVarsh (2019).[19,31,40,41] Regarding individual teeth, we found the occurrence of pulpal radiopacities being 8.3% (1031/12047) in DPR images, and 10.6% (1326/12407) in DPA images. This finding is also similar with those reports by Ranjitkar et al. (2002), AlNazhan & Sl-Shamrani (2011), Jayam et al. (2017), Kuzekanani et al. (2018).[33,35,42,43] The findings supported a significant difference between two assessed radiographic techniques (Table 1) ($P < 0.01$).

Robertson et al., in 1997 and Holan in 1998 analyzed the incidence of calcific metamorphosis using radiographic techniques and they found a significant correlation between calcification and dental trauma.[10,11] Other researchers reported the incidence of calcified bodies in the dental pulp increased with age.[1,19,27] Our results are in line with their findings. In our study population including four age groups (from 17 to >60 years of age) and results indicated the occurrence of pulp stone calcifications in the dental pulps of periodontal disease increased with old age

groups, particularly those aged >40 years (Table 1). Over 90.6% (935/1031) in DPR images, and 89.7% (1192/1326) in DPA images had pulp stone calcifications identified in those older age groups ($p < 0.001$). Studies of Hillmann & Geurtsen (1997), Fetami et al. (2012) and Chen & Huang (2016) reported higher rate pulpal calcifications in elderly patients with periodontal disease.[7,12,13] These authors also suggested that the frequency, duration and intensity of chronic irritations being causative factors for such calcifications. Consistent with that, we found a high incidence of pulp stone calcifications in periodontally involved teeth up to 58.0%–78.8% respectively ($p < 0.006$).

In this study, we found no correlation between gender and pulp cavity calcification ($p > 0.05$). Our finding is in line with the work of Sayegh & Reed (1968) and Stroner & Van Cura (1984).[1,4] Furthermore, the tendency we found for a higher chance of pulp calcifications in molar teeth also agrees with the most recent studies.[19,32,33,35,40–42] We confirmed the higher prevalence of calcifications in molar teeth (65.1% in DPA and 44.1% in DPA) compared with bicuspid (23.3% in DPA and 33.1% in DPA) and incisors (11.4% in DPR and 22.4% in DPA) (Table 1). The underlying casuse may be related to their large pulp chamber and space in the dentition, and hence greater chance to be injured and damaged during daily mastication, leading to formation of calcified stones.

In conclusion, our results are in support of pulpal calcifications commonly occurring in human dental pulp tissue. Other findings are the prevalence of pulp stone calcifications in a group of periodontal patients in Taiwan Chinese population was 58.0% with digital panoramic examination, and 74.8% with digital periapical radiographic examination. Both prevalence rates were higher than other populations such as Libyan (Alawjali 2019), Indian (Yousuf et al., 2018; Sandhu et al., 2018), Iranian (Hassanabadi et al., 2018; Kuzekanani et al., 2018), Nepal (Jayam et al., 2017), Turkish (Turkal et al., 2013; Gulsahi et al., 2009), Saudi Arabia (AlNazhan & Sl-Shamrani 2011; Sadoon et al., 2019), and Iraqi (Al-Ghurabi & Najm (2012) (Table 3).[26,28,29,32–35,37,38,43,44] As pulp stone calcifications are likely dystrophic and degenerative manifestations, and may develop in different patterns and number and/or size due to chronic local irritation such as aging, periodontal disease, and dental trauma. In addition, we found pulpal calcifications in maxillary molar teeth being more common than in bicuspids and incisors (Table 1). Our findings of incidence of pulp calcification associated with chronic tissue inflammation (e.g., periodontal disease) which likely plays a key role in the formation of pulpal calcification. Since conflicting reports in the literature exist regarding the association between pulp calcification and systemic disturbances. Further studies on longitudinal data of larger samples would help to clarify potential correlation between systemic and medical disorders such as coronary artery disease, diabetes mellitus and renal dysfunction.

Declaration of competing interest

The authors gave no conflicts of interest relevant to this article.

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