

Aline Maria do COUTO<sup>(a)</sup>   
Daniela Pereira MEIRELLES<sup>(a)</sup>   
Alline Teixeira VALERIANO<sup>(a)</sup>   
Douglas Silva de ALMEIDA<sup>(b)</sup>   
Èmile de MORAES<sup>(b)</sup>   
Sandra Beatriz Chaves  
TARQUINIO<sup>(b)</sup>   
Aline Carvalho BATISTA<sup>(c)</sup>   
Elismauro Francisco de  
MENDONÇA<sup>(c)</sup>   
Nádia do Lago COSTA<sup>(c)</sup>   
Pollianna Muniz ALVES<sup>(d)</sup>   
Cassiano Francisco Weege  
NONAKA<sup>(d)</sup>   
Lucas Guimarães ABREU<sup>(e)</sup>   
Maria Cássia Ferreira de  
AGUIAR<sup>(e)</sup> 

<sup>(a)</sup>Universidade Federal de Minas Gerais – UFMG, School of Dentistry, Department of Oral Surgery and Pathology, Belo Horizonte, MG, Brazil.

<sup>(b)</sup>Universidade Federal de Pelotas – UFPel, School of Dentistry, Department of Semiology and Clinics, Pelotas, RS, Brazil.

<sup>(c)</sup>Universidade Federal de Goiás – UFGO, School of Dentistry, Department of Stomatology (Oral Pathology), Goiânia GO, Brazil.

<sup>(d)</sup>Universidade Estadual da Paraíba – UFPB, School of Dentistry, Department of Dentistry, Campina Grande PB, Brazil.

<sup>(e)</sup>Universidade Federal de Minas Gerais – UFMG, School of Dentistry, Department of Pediatric Dentistry and Orthodontics, Belo Horizonte, MG, Brazil.

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**Corresponding Author:**

Aline Maria do Couto  
E-mail: alinemariacouto@hotmail.com

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## Chronic inflammatory periapical diseases: a Brazilian multicenter study of 10,381 cases and literature review

**Abstract:** The aim of this study was to investigate the epidemiological and clinical characteristics of chronic inflammatory periapical diseases in different regions of Brazil and to compare with data from the literature. A multicenter study was carried out in four Brazilian referral centers in oral diagnosis. Histopathological records were reviewed, and all cases diagnosed microscopically as periapical granuloma, radicular cyst, and periapical abscess were included. Demographic and clinical data were collected. Descriptive statistics and Pearson's chi-square test were performed. A total of 10,381 cases of chronic inflammatory periapical diseases were found (13.8% of 74,931 archived specimens) over a period of 65 years. Radicular cysts were the most common lesion (59.9%). Women (56.1%) with a mean age of 37.01 years old (range 13 to 100 ± 14.42) and people of white skin color (59.2%) were the most affected individuals by chronic inflammatory periapical diseases. The lesions were generally asymptomatic (28.1%), located in the maxilla (60.1%), and posterior region (49.8%). The radicular cysts were larger when compared to periapical granulomas ( $p < 0.001$ ). The disagreement between the clinical and histopathological diagnoses was higher when the final diagnosis was a periapical granuloma ( $p < 0.001$ ). Chronic inflammatory periapical diseases continue to be common lesions affecting mainly adults. This should be a consequence of the burden of untreated caries in permanent teeth. Women are more affected and radicular cyst was the most common lesion.

**Keywords:** Periapical Diseases; Periapical Granuloma; Radicular Cyst; Periapical Abscess; Epidemiology.

## Introduction

In recent years, the global prevalence of untreated caries in permanent teeth has stagnated worldwide.<sup>1</sup> However, dental caries remains the most common oral disease affecting the world population.<sup>2</sup> This situation is not different in Brazil, even though significant advances in dental caries prevention and control has taken place.<sup>3</sup> The main consequence of untreated caries is pulp necrosis.<sup>4</sup> Therefore, along with periodontitis, dental caries is the main cause of tooth loss in adult patients.<sup>5</sup>

Periapical disease is an inflammatory disease around the apex of the root of a tooth caused by an infection in the root canal.<sup>6,7</sup> Although trauma and iatrogenic factors may lead to this outcome, dental caries is the main cause



of pulp infection.<sup>4,8</sup> Periapical disease is characterized by local inflammation, bone and tissues destruction resulting in periapical lesions, usually classified in accordance with their histological structure in periapical granulomas, radicular cysts, and periapical abscesses.<sup>6,9</sup> Briefly, periapical granulomas are histopathologically constituted by “presence of a granulomatous tissue predominantly infiltrated with lymphocytes, plasma cells and macrophages”<sup>6</sup> and “may be non-epithelialized or epithelialized.”<sup>6</sup> Radicular cysts are constituted by “a distinct epithelium-lined pathological cavity.”<sup>6</sup> Periapical abscesses are lesions constituted by “presence of a distinct collection of polymorphonuclear leukocytes” and may be epithelialized or non-epithelialized.<sup>10</sup>

Epidemiological clinical studies in different populations show periapical disease as a widespread condition in many countries.<sup>11,12,13,14,15</sup> However, there is an expressive variability in the results, particularly in relation to the frequency of these lesions. Considering that Brazil is a continental country, with marked social differences among regions and inequalities associated with oral health care,<sup>3</sup> a multicenter study in this country may depict the epidemiological and clinical aspects of chronic inflammatory periapical disease more appropriately. In addition, this study may contribute to the knowledge of specific features of periapical disease and the association of this outcome with demographic and clinical characteristics of the affected population.

Thus, the aim of this multicenter study was to investigate the epidemiological and clinical characteristics of chronic inflammatory periapical diseases including periapical granulomas, radicular cysts, and periapical abscesses in a sample of Brazilians, and to compare these features with data retrieved in a literature review.

## Methodology

### Multicenter study

#### Ethical issues and study design

A multicenter retrospective study (1952–2017) was conducted in four institutional referral centers in oral diagnosis in different geographic regions in Brazil: Universidade Estadual da Paraíba (UEPB, northeast region), Universidade Federal de Goiás (UFG, mid-west region), Universidade Federal de Minas Gerais

(UFMG, southeast region) and Universidade Federal de Pelotas (UFPel, southern region). The study was approved by the Committee of Ethics on Research of the Universidade Federal de Minas Gerais (protocol CAAE 87761518.7.1001.5149). Patient’s anonymity was guaranteed according to the Helsinki Declaration.

### Sample

Histopathological records (n = 74,931) of oral and maxillofacial lesions registered at the Oral and Maxillofacial Pathology services of all the participating institutions were reviewed without any date restrictions. All cases with a microscopic diagnosis of a periapical granuloma, radicular cyst, or periapical abscess<sup>6</sup> were selected. The terms used for this study were periapical granuloma, apical granuloma, dental granuloma, radicular granuloma, dental radicular granuloma, radicular cyst, periapical cyst, apical periodontal cyst, dental cyst, apical cyst, dental radicular cyst, residual cyst, residual radicular cyst, residual periapical cyst, residual dental radicular cyst, periapical abscess, dental radicular abscess, dental abscess, and dentoalveolar abscess. Cases without a histopathological diagnosis were excluded, as well as cases affecting individuals ≤ 12 years because of the mixed dentition, for which a separate analysis is more appropriate.

The following demographic and clinical data were collected from the patient records: sex (female or male), age (13–19, 20–29, 30–39, 40–49, 50–59, or ≥ 60), skin color (white or non-white), symptoms (asymptomatic or symptomatic), lesion duration (0–6 months, 7–12 months, or more than 1 year), lesion size (≤ 10 mm or > 10 mm), lesion location (maxilla or mandible and anterior, posterior, or both) and agreement between the clinical and histopathological diagnoses (disagreement, agreement, or nonspecific clinical diagnosis).

### Statistical analysis of data

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 22.0 (SPSS Inc, Armonk, USA). Descriptive statistics and bivariate analyses using Pearson’s Chi-square test were carried out. The z-test to compare the proportions in the columns and the Bonferroni correction were employed for variables with more than two categories. *P* values < 0.05 were considered statistically significant.

## Literature review

### Eligibility criteria

A literature review was carried out to retrieve retrospective studies investigating the frequency of periapical diseases microscopically diagnosed in Oral and Maxillofacial Pathology services. Inclusion criteria were: studies assessing cases with a microscopic diagnosis of periapical granuloma, radicular cyst, or periapical abscess and studies in English, Portuguese, or Spanish published within the last 20 years (1999–2019). Case reports or series with less than 10 cases, *in vitro* studies, immunohistochemistry and microbiology studies, animal studies, studies with cadaver, prospective studies, studies that included restricted age groups (for example children/adolescents or older people), studies that did not report the total sample size, reviews, editorials, letters, abstracts of scientific meetings, and book chapters were excluded.

### Information source

The electronic search was performed in PubMed (National Library of Medicine), in September/2019 using the following search strategy: apical periodontitis OR periapical periodontitis OR periapical lesion OR apical lesion OR periapical granuloma OR apical granuloma OR dental granuloma OR radicular granuloma OR dental radicular granuloma OR radicular cyst OR periapical cyst OR apical periodontal cyst OR dental cyst OR apical cyst OR dental radicular cyst OR residual cyst OR residual radicular cyst OR residual periapical cyst OR residual dental radicular cyst OR periapical abscess OR dental radicular abscess OR dental abscess OR dentoalveolar abscess AND

histopathological OR histopathologic OR microscopic OR microscopy OR slide.

### Study selection

The selection of studies performed by two reviewers (AMC and LGA) was divided into two phases. In Phase 1, titles/abstracts that fulfilled the eligibility criteria were included. In case of doubt, the full text was retrieved for evaluation in Phase 2 to determine whether the reference would be included or not.

### Data extraction

Data extracted from the included articles were: authors, year of publication, country where the study was conducted, period of investigation (in years), sample size (total), group of oral lesions included, frequency of periapical diseases - periapical granuloma, radicular cyst and periapical abscess - (% total), and frequency of periapical diseases - periapical granuloma, radicular cyst, and periapical abscess - (% in group of oral lesions included).

## Results

### Multicenter study

Among the 74,931 records, 13.8% (10,381 samples) were cases of chronic inflammatory periapical diseases in individuals  $\geq 13$  years old. Considering the specific diagnosis, radicular cysts represented 8.2%, periapical granulomas represented 5.4%, and periapical abscesses, 0.07% of all records. The cases of periapical diseases were distributed within the institutions as follows: 286 in UEPB, 903 in UFG, 4,388 in UFMG, and 4,804 in UFPel. Table 1 shows the frequency of periapical diseases per institution and in general.

**Table 1.** Frequency of chronic inflammatory periapical diseases.

Institution (geographical region of Brazil)	Period investigated	Biopsied lesions in the studied period	Number of diagnosis
			n (%)
UEPB (northeast)	2011-2017	2,793	286 (10.2)
UFG (mid-west)	1996-2017	10,958	903 (8.2)
UFMG (southeast)	1952-2017	36,61	4,388 (11.9)
UFPel (south)	1959-2017	24,57	4,804 (19.5)
Total		74,931	10,381 (13.8)

UEPB: Universidade Estadual da Paraíba; UFG: Universidade Federal de Goiás; UFMG: Universidade Federal de Minas Gerais; UFPel: Universidade Federal de Pelotas.

Clinical and demographic data of lesions are presented in Table 2. In all referral centers, women [(5,821 cases (56.1%)] were more affected than men. The mean age of the patients was 37.01 years old ( $\pm 14.42$ ) and ranged between 13 and 100 years. A total of 2,376 (22.9%) cases occurred in individuals between 30 and 39 years old. In all referral centers, the predominant skin color of the affected individuals was white [6,148 cases (59.2%)], except for UEPB, where non-white individuals were the most affected [159 cases (68.2%)].

The frequency of lesions in the referral centers followed the same tendency. The most frequent lesions were radicular cysts [6,215 cases (59.9%)], followed by periapical granulomas [4,110 cases (39.6%)]. Periapical abscesses represented only 0.5% of the total sample. Among the 6,215 cases of radicular cysts, 602 (5.8%) were residual cysts. The lesions were predominantly asymptomatic [2,921 cases (28.1%)] with a duration of more than one year [1,378 cases (13.3%)], and a size of  $\leq 10$  mm [2,617 cases (25.2%)]. The mean lesion size was 12.58 mm ( $\pm 13.68$ ) and ranged between 0.1 mm and 150.0 mm. Regarding the anatomical location, the maxilla [6,241 cases (60.1%)] and the posterior region [5,172 cases (49.8%)] had the highest frequency of cases.

Agreement between the clinical and histopathological diagnoses occurred in 5,865 (56.5%) cases, disagreement in 1,933 (18.6%), missing clinical diagnostic information in 1,006 (9.7%) cases, and 1,577 (15.2%) of the cases had a non-specific clinical diagnosis, making the analysis unfeasible. Table 3 shows the clinical diagnoses of the cases, for which there was disagreement with the histopathological diagnosis. For the cases in which the histopathological diagnosis was a periapical granuloma, the most frequent diagnostic hypothesis was a radicular cyst [1,278 cases (94.7%)]. For the cases of a radicular cyst, the most frequent hypothesis was a periapical granuloma [352 cases (62.4%)] and an odontogenic keratocyst [62 cases (11.0%)]. Finally, for cases of a periapical abscess, the most frequent hypothesis was a radicular cyst [12 cases (60.0%)].

Bivariate analyses results comparing periapical granulomas and radicular cysts are shown in Table 4. There was a significantly higher frequency

**Table 2.** Distribution of the clinical and demographic features of 10,381 cases of chronic inflammatory periapical disease.

Variables	n (%)
<b>Sex</b>	
Female	5,821 (56.1)
Male	4,321 (41.6)
Missing	239 (2.3)
<b>Age (years)</b>	
13–19	999 (9.6)
20–29	2,258 (21.8)
30–39	2,376 (22.9)
40–49	1,886 (18.2)
50–59	1,175 (11.3)
$\geq 60$	722 (7.0)
Missing	965 (9.3)
<b>Skin color</b>	
White	6,148 (59.2)
Non-white	2,616 (25.2)
Missing	1,617 (15.6)
<b>Histopathological diagnosis</b>	
Periapical granuloma	4,110 (39.6)
Radicular cyst	6,215 (59.9)
Periapical abscess	56 (0.5)
<b>Symptoms</b>	
Asymptomatic	2,921 (28.1)
Symptomatic	1,431 (13.8)
Missing	6,029 (58.1)
<b>Lesion duration</b>	
0–6 months	493 (4.7)
7–12 months	508 (4.9)
More than 1 year	1,378 (13.3)
Missing	8,002 (77.1)
<b>Size</b>	
$\leq 10$ mm	2,617 (25.2)
$> 10$ mm	1,270 (12.2)
Missing	6,494 (62.6)
<b>Lesion location I</b>	
Maxilla	6,241 (60.1)
Mandible	3,440 (33.1)
Missing	700 (6.7)
<b>Lesion location II</b>	
Anterior	3,719 (35.8)
Posterior	5,172 (49.8)
Both	569 (5.5)
Missing	921 (8.9)
<b>Agreement between clinical and histopathological diagnosis</b>	
Disagreement	1,933 (18.6)
Agreement	5,865 (56.5)
Nonspecific clinical diagnosis	1,577 (15.2)
Missing	1,006 (9.7)

**Table 3.** Clinical diagnosis of cases with disagreement between the clinical and histopathological diagnosis (n = 1,933).

Variable	Histopathological diagnosis		
	Periapical granuloma (n = 1,349)	Radicular cyst (n = 564)	Periapical abscess (n = 20)
	n (%)	n (%)	n (%)
Clinical diagnosis			
Periapical granuloma	-	352 (62.4)	4 (20.0)
Radicular cyst	1,278 (94.7)	-	12 (60.0)
Periapical granuloma or radicular cyst	-	-	4 (20.0)
Periapical abscess	22 (1.6)	25 (4.4)	-
Osteomyelitis	4 (0.3)	12 (2.1)	0 (0.0)
Bone sequestration	1 (0.1)	2 (0.4)	0 (0.0)
Bisphosphonate associated osteonecrosis	0 (0.0)	1 (0.2)	0 (0.0)
Foreign body reaction	1 (0.1)	0 (0.0)	0 (0.0)
Periodontal lesion	2 (0.1)	5 (0.9)	0 (0.0)
Endodontic-periodontal lesion	3 (0.2)	6 (1.1)	0 (0.0)
Pyogenic granuloma	0 (0.0)	6 (1.1)	0 (0.0)
Granulomatous epulis	1 (0.1)	0 (0.0)	0 (0.0)
Central Giant Cell Granuloma	1 (0.1)	2 (0.4)	0 (0.0)
Dentigerous cyst	7 (0.5)	20 (3.5)	0 (0.0)
Odontogenic keratocyst	6 (0.4)	62 (11.0)	0 (0.0)
Periodontal cyst	9 (0.7)	25 (4.4)	0 (0.0)
Paradentary cyst	1 (0.1)	6 (1.1)	0 (0.0)
Globule-maxillary cyst	3 (0.2)	5 (0.9)	0 (0.0)
Nasopalatine duct cyst	1 (0.1)	3 (0.5)	0 (0.0)
Median palatine cyst	0 (0.0)	1 (0.2)	0 (0.0)
Median mandibular cyst	0 (0.0)	2 (0.4)	0 (0.0)
Maxillary sinus cyst	0 (0.0)	1 (0.2)	0 (0.0)
Mucous retention cyst	0 (0.0)	2 (0.4)	0 (0.0)
Epidermoid cyst	1 (0.1)	0 (0.0)	0 (0.0)
Simple bone cyst	0 (0.0)	2 (0.4)	0 (0.0)
Fibrous dysplasia	1 (0.1)	1 (0.2)	0 (0.0)
Cemento-osseous dysplasia	0 (0.0)	2 (0.4)	0 (0.0)
Central odontogenic fibroma	1 (0.1)	0 (0.0)	0 (0.0)
Neurofibroma	0 (0.0)	1 (0.2)	0 (0.0)
Ameloblastoma	4 (0.3)	9 (1.6)	0 (0.0)
Squamous odontogenic tumor	0 (0.0)	1 (0.2)	0 (0.0)
Odontoma	0 (0.0)	2 (0.4)	0 (0.0)
Odontogenic myxoma	0 (0.0)	4 (0.7)	0 (0.0)
Cementoma	0 (0.0)	1 (0.2)	0 (0.0)
Brown Tumor	0 (0.0)	1 (0.2)	0 (0.0)
Papilloma	1 (0.1)	0 (0.0)	0 (0.0)
Blastomycosis	1 (0.1)	2 (0.4)	0 (0.0)

of women diagnosed with periapical granulomas and radicular cysts ( $p < 0.001$ ) and a significantly higher frequency of radicular cysts diagnosed in patients aged 13–19 and 50–59 years in relation to periapical granulomas ( $p < 0.001$ ).

Although uncommon, symptomatology was more frequently reported among cases of cysts than among cases of granulomas ( $p < 0.027$ ). Cysts were also bigger than granulomas ( $p < 0.001$ ). The mean size of periapical granulomas was 7.22 mm

**Table 4.** Bivariate analyses of 10,325\* periapical granulomas and radicular cysts.

Variables	Histopathological diagnosis		p-value**
	Periapical granuloma (n = 4,110)	Radicular cyst (n = 6,215)	
	n (%)	n (%)	
<b>Sex</b>			
Female	2,528 (63.3)	3,258 (53.5)	
Male	1,468 (36.7)	2,833 (46.5)	< 0.001
<b>Age (years)</b>			
13–19	431 (11.6) <sup>a</sup>	558 (9.9) <sup>b</sup>	
20–29	927 (24.9)	1,314 (23.3)	
30–39	966 (25.9)	1,402 (24.9)	
40–49	725 (19.5)	1,154 (20.5)	
50–59	414 (11.1) <sup>a</sup>	755 (13.4) <sup>b</sup>	
≥ 60	262 (7.0)	457 (8.1)	< 0.001
<b>Skin color</b>			
White	2,435 (69.6)	3,678 (70.5)	
Non-white	1,064 (30.4)	1,538 (29.5)	0.364
<b>Symptoms</b>			
Asymptomatic	1,044 (65.0)	1,863 (68.3)	
Symptomatic	561 (35.0)	863 (31.7)	0.027
<b>Lesion duration</b>			
0–6 months	185 (20.2)	303 (20.9)	
7–12 months	188 (20.5)	319 (22.0)	
More than 1 year	545 (59.4)	830 (57.2)	0.548
<b>Size</b>			
≤ 10 mm	1,215 (87.4)	1,386 (55.9)	
> 10 mm	175 (12.6)	1,094 (44.1)	< 0.001
<b>Lesion location I</b>			
Maxilla	2,475 (65.3)	3,734 (63.9)	
Mandible	1,314 (34.7)	2,108 (36.1)	0.163
<b>Lesion location II</b>			
Anterior	1,443 (38.1)	2,257 (40.1)	
Posterior	2,283 (60.3) <sup>a</sup>	2,859 (50.8) <sup>b</sup>	
Both	58 (1.5) <sup>a</sup>	511 (9.1) <sup>b</sup>	< 0.001
<b>Agreement between clinical and histopathological diagnosis</b>			
Disagreement	1,349 (36.7) <sup>a</sup>	564 (10.0) <sup>b</sup>	
Agreement	1,537 (41.8) <sup>a</sup>	4,320 (76.5) <sup>b</sup>	
Nonspecific clinical diagnosis	792 (21.5) <sup>a</sup>	763 (13.5) <sup>b</sup>	< 0.001

\*56 cases of periapical abscesses were not included in the bivariate analyses because of their low frequency (0.5%). \*\*Pearson Chi-square test (Significance level  $p < 0.05$ ). Different letters indicate a statistical difference using the z-test and Bonferroni correction (significance level of  $p < 0.05$ ).

(± 8.24) and ranged between 0.2 mm and 150.0 mm, while the mean size of the cysts was 15.62 mm (±15.16) and ranged between 0.1 mm and 150.0 mm. The posterior region of the jaw was the most frequent location of both periapical granulomas and radicular cysts, with cysts outnumbering granulomas ( $p < 0.001$ ). The disagreement between clinical and

histopathological diagnoses was more common when the histopathological diagnosis was a periapical granuloma ( $p < 0.001$ ).

### Literature review

In the literature review, 1,786 articles were retrieved. The eligibility criteria were applied and 13 articles

were selected.<sup>12,16-27</sup> Considering the total sample of the studies, the frequency of periapical granuloma varied between 0.007<sup>20</sup> and 17.3%,<sup>19</sup> radicular cyst between 0.03<sup>20</sup> and 22.7%,<sup>19</sup> and periapical abscess between 0.4<sup>25</sup> and 0.5%.<sup>12</sup>

The frequency of radicular cysts in studies that included jaw lesions ranged from 24.7<sup>25</sup> to 29.9%.<sup>19</sup> Considering jaw intraosseous lesions, that frequency ranged from 17.8<sup>20</sup> to 19.6%<sup>16</sup> and between odontogenic cysts ranged from 35.1<sup>23</sup> to 54.1%.<sup>17</sup> Considering the radiolucent inflammatory jaw lesions, the frequency of periapical granuloma was 59.7% and of radicular cyst 29.2%<sup>12</sup> (Table 5).

## Discussion

This multicenter study showed that chronic inflammatory periapical diseases are common, representing 13.8% of the lesions diagnosed in the referral centers where data for the present study were collected. Radicular cysts accounted for 8.29%, periapical granulomas accounted for 5.48%, and periapical abscesses accounted for 0.07%. The frequency of lesions was higher in the southern region (19.5%). In agreement with these results, most studies included in the literature review also demonstrated an expressive frequency of periapical diseases in Oral and Maxillofacial Pathology services. The association of dental caries with periapical disease is helpful in the understanding of these results.<sup>4</sup> Although dental caries may develop later in life with a reduction in childhood prevalence, there is a burden among adults with economic and social consequences.<sup>1</sup> Therefore, effective allocation of resources in preventive or therapeutic actions aiming to tackle dental caries in individuals of all ages would prevent the development of chronic periapical disease in Brazil and elsewhere.

In the present study, radicular cysts (59.9%) were more frequent than periapical granulomas (39.6%) agreeing with what has been described in other studies.<sup>11,15,28</sup> Radicular cysts were the most frequent chronic inflammatory periapical disease. Probably, conventional endodontic treatment is more successful for periapical granulomas than for radicular cysts<sup>15</sup> and after periapical surgery, the

radicular cysts are the periapical lesions that present worse prognosis.<sup>29</sup> Therefore, surgical treatment with posterior histopathologic exam is employed more frequently for the treatment of radicular cysts<sup>15</sup>, explaining the frequency results of this study. However, there are also studies describing periapical granulomas as the most common periapical disease.<sup>30,31</sup> Comparisons among studies are difficult due to differences in sample size, type of study, nomenclature, and histopathological criteria in the differentiation of radicular cysts and periapical granulomas.<sup>11-15,32</sup> Finally, in this study, periapical abscesses were extremely uncommon lesions, similar to findings published elsewhere.<sup>12,14</sup>

Another interesting aspect is the tendency to surgically remove larger lesions, while minor lesions are usually treated without surgery.<sup>33</sup> Usually, larger lesions are radicular cysts.<sup>34</sup> Indeed, in this study, a significantly higher frequency of radicular cysts measuring more than 10 mm was observed. Most periapical granulomas (87.4%) had a mean size of 10 mm and cysts were approximately double the size of granulomas as observed by other authors.<sup>15</sup>

It is interesting to observe that the results were quite similar among the referral centers. In all Oral and Maxillofacial Pathology facilities, women were more affected by chronic inflammatory periapical disease than men. Periapical granulomas and radicular cysts, analyzed separately, had higher frequency among women, which is similar to the findings of another Brazilian study.<sup>15</sup> Other studies, though, showed that radicular cysts had a predilection for males.<sup>12,35</sup> The fact that chronic inflammatory periapical diseases are more frequent in women does not necessarily reflect a genetic predisposition for the development of these lesions or the influence of sex. The most likely explanation is the greater concern of women regarding their oral health, which ultimately has an impact on their treatment seeking.<sup>36</sup>

The mean age of the patients affected by chronic inflammatory periapical disease was 37.01 years old. The mean age varies across studies, but there is a predominance of cases affecting individuals in their third and fourth decades of life.<sup>11,13,15,31</sup> These

**Table 5.** Reported frequency of periapical diseases in the literature.

Authors, year and country	Period (years)	Sample size (total)	Group of oral lesions included (n)	Frequency of periapical diseases (% total)	Frequency of periapical diseases (% in group of oral lesions included)
Present study	1952 to 2017	74,931	Periapical diseases (n = 10,381)	Periapical granuloma (n = 4,110, 5.4%); Radicular cyst (n = 6,215, 8.2%); Periapical abscess (n = 56, 0.07%)	Periapical granuloma (n = 4,110, 39.6%); Radicular cyst (n = 6,215, 59.9%); Periapical abscess (n = 56, 0.5%)
Farias et al., 2019, <sup>16</sup> Brazil	2006 to 2017	2,051	Intraosseous lesions of the stomatognathic complex (n = 290)	Periapical granuloma (n = 26, 1.2%*) Radicular cyst (n = 57, 2.7%*)	Periapical granuloma (n = 26, 8.9%*) Radicular cyst (n = 57, 19.6%*)
Villasis-Sarmiento et al., 2017, <sup>17</sup> Mexico	2000 to 2013	10,97	Odontogenic cysts (n = 753)	Radicular cyst (n = 408, 3.7%); Residual cyst (n = 18, 0.1%*)	Radicular cyst (n = 408, 54.1%); Residual cyst (n = 18, 2.3%)
Deepthi et al., 2016, <sup>18</sup> India	1998 to 2012	7,117	Odontogenic cysts and tumors (n = 1,177)	Radicular cyst: (n = 655, 9.2%*); Residual cyst (n = 44, 0.6%*)	Radicular cyst: (n = 655, 55.6%*); Residual cyst (n = 44, 3.7%*)
Peker et al., 2016, <sup>19</sup> Turkey	2008 to 2013	1,938	Jaw lesions (n = 1,473)	Periapical granuloma (n = 337, 17.3%*); Radicular cyst (n = 440, 22.7%*); Residual cyst (n = 76, 3.9%*)	Periapical granuloma (n = 337, 22.9%); Radicular cyst (n = 440, 29.9%); Residual cyst (n = 76, 5.2%)
Jamshidi et al., 2015, <sup>20</sup> Iran	1990 to 2010	142,865	Jaw intraosseous lesions (n = 284)	Periapical granuloma (n = 11, 0.007%*) Radicular cyst (n = 51, 0.03%*); Residual cyst (n = 3, 0.002%*)	Periapical granuloma (n = 11, 3.8%) Radicular cyst (n = 51, 17.8%); Residual cyst (n = 3, 1.0%)
Akinyamoju et al., 2014 <sup>21</sup> , Nigeria	1990 to 2012	1,877	Periapical lesions (endodontic and non-endodontic) (n = 104)	Periapical granuloma (n = 71, 3.7%*); Radicular cyst (n = 31, 1.6%*)	Periapical granuloma (n = 71, 68.3%); Radicular cyst (n = 31, 29.8%)
Alcantara et al., 2013, <sup>22</sup> Brazil	2000 to 2010	3,446*	Radicular cyst	Radicular cyst (n = 214, 6.2%)	Not applicable (Only one group included)
Khosravi et al., 2013, <sup>23</sup> Iran	1988 to 2010	7,412	Odontogenic cysts (n = 1,603)	Radicular cyst (n = 563, 7.5%*) Residual cyst (n = 208, 2.8%*)	Radicular cyst (n = 563, 35.1%); Residual cyst (n = 208, 12.9%)
Butt et al., 2011, <sup>24</sup> Kenya	1991 to 2010	4,257	Odontogenic and nonodontogenic cysts (n = 194)	Radicular cyst (n = 43, 1.0%*)	Radicular cyst (n = 43, 22.1%)
Ali, 2011, <sup>25</sup> Kuwait	2004 to 2009	1,28	Jaw lesions (n = 385)	Chronic apical periodontitis (n = 59, 4.6%*); Radicular cyst (n = 95, 7.4%*); Residual cyst (n = 8, 0.6%*); Dental abscess (n = 6, 0.4%*)	Chronic apical periodontitis (n = 59, 15.3%); Radicular cyst (n = 95, 24.7%); Residual cyst (n = 8, 2.0%*); Dental abscess (n = 6, 1.5%*)
Becconsall-Ryan et al., 2010, <sup>12</sup> New Zealand	1986 to 2006	17,038	Radiolucent inflammatory jaw lesions (n = 3,626)	Periapical granuloma (n = 2,165, 12.7%*); Radicular cyst (n = 1,057, 6.2%*); Periapical abscess (n = 88, 0.5%*)	Periapical granuloma (n = 2,165, 59.7%); Radicular cyst (n = 1,057, 29.2%); Periapical abscess (n = 88, 2.4%)
Núñez-Urrutia et al., 2010, <sup>26</sup> Spain	1997 to 2006	1,235	Odontogenic cysts (n = 418)	Radicular cyst (n = 210, 17.0%*); Residual cyst (n = 18, 1.4%*)	Radicular cyst (n = 210, 50.2%); Residual cyst (n = 18, 4.3%)
Ledesma-Montes, et al., 2000, <sup>27</sup> Mexico	1986 to 1996	3,865	Odontogenic cysts (n = 304)	Radicular cyst (n = 118, 3.0%*); Residual cyst (n = 15, 0.3%*)	Radicular cyst (n = 118, 38.8%); Residual cyst (n = 15, 4.9%)

\*Calculated according to the data presented in the article.



findings are possibly associated with the highest prevalence of untreated dental caries in young adults, leading to the development of periapical disease.<sup>1</sup> On the other hand, as observed by other authors, these lesions are rare among adults older than 60 years.<sup>37</sup> This probably occurs because tooth extraction, as an alternative to conventional endodontic treatment, is carried out more frequently in the elderly than in younger patients.<sup>37</sup>

Most patients diagnosed with chronic inflammatory periapical disease were white. However, since the vast majority of cases were from the South (46.3%) and Southeast of Brazil (42.3%), these data may be overestimated since the population of those regions is predominantly white.<sup>38</sup> However, it is important to emphasize that the concentration of cases in the south and southeast regions (88.6%) may also reflect a situation of inequality in the access to oral health services in Brazil. This reinforces the need for public policies that make access to this type of treatment universal in all regions of the country.

Regarding clinical characteristics, most cases of chronic inflammatory periapical disease had a long evolution, with a duration of more than one year and absence of symptomatology. The symptomatic cases of the study (13.8%) occurred due to an acute exacerbation of inflammation.<sup>8</sup> It is interesting to observe that the occurrence of symptoms was higher in radicular cysts compared to periapical granulomas. Radicular cysts are bigger than periapical granulomas and can cause bone expansion, pain, and discomfort.<sup>15,39</sup>

The permanent first molars are the teeth most affected by dental caries.<sup>40</sup> In this sense, molars and teeth with dental caries are at a higher risk for periapical disease.<sup>41</sup> In the present study, most cases of periapical granulomas and radicular cysts had a predilection for the posterior region. Permanent molars are the first teeth to erupt and this makes them more susceptible to dental caries, pulp infection, and periapical disease.<sup>41</sup> On the other hand, other authors reported that the most common region for periapical granulomas and radicular cysts was the anterior maxilla.<sup>11,15</sup> Aesthetic reasons can explain these results since patients are concerned in maintaining

their anterior teeth, even though endodontic therapy was unsatisfactory.<sup>42</sup>

In present study, agreement analyses between clinical and histopathological diagnoses had three outcomes: disagreements within the spectrum of periapical inflammatory diseases (for example, cysts diagnosed as granulomas or granulomas diagnosed as cysts); periapical diseases diagnosed as other bone pathologies including cysts and tumors; and periapical diseases diagnosed as lesions of the mucosa. All these situations denote failure in the diagnosis based only in one aspect of the disease; clinical or radiographic. However, for the establishment of the initial diagnosis of any lesion, the correlation of both aspects is necessary.<sup>43</sup> Pulp vitality test is fundamental in the establishment of a diagnosis of periapical disease<sup>44</sup> and unfortunately, this tool is frequently ignored by practitioners. In most cases, the initial diagnosis was conducted only by radiographic exam. Although periapical radiolucency can be interpreted as many different lesions, the inflammatory lesion of endodontic origin is the most common and continues to be the first hypothesis.<sup>45</sup> The diagnostic agreement was higher when the histopathological diagnosis was a radicular cyst. Despite this finding, the radiographic differentiation of inflammatory periapical disease is difficult, particularly when represented by small and poorly defined radiolucent areas.<sup>46</sup> Thus, the most appropriate diagnostic tool to differentiate among these lesions is biopsy followed by a histopathological evaluation.<sup>12,47</sup>

This study has limitations. Although the study included referral centers of different geographic regions of Brazil, these data may not be representative of the entire country. Thus, caution is required in extrapolating the findings to the rest of the population.<sup>48</sup> In addition, a possible social bias may have occurred since the samples were obtained from public Brazilian universities, where individuals of a lower socioeconomic level seek treatment. Moreover, the histological slides were not reviewed to confirm diagnosis.

The present study evaluated the epidemiological and clinical characteristics of chronic inflammatory periapical disease. The strengths of this study are the long period of investigation, the multicenter

approach, including different geographic regions of Brazil, and the large sample size.

## Conclusions

Chronic inflammatory periapical diseases were common in the Brazilian Oral and Maxillofacial Pathology services. Women, young adults, and people of white skin color were the most affected patients.

Radicular cysts were the most frequent lesion. Chronic inflammatory periapical diseases were

asymptomatic, with maxilla and posterior region being the most affected anatomical locations.

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