UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

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# AVALIAÇÃO CLÍNICA E RADIOGRÁFICA DE PACIENTES AFETADOS POR DISPLASIA ÓSSEA FLORIDA – ESTUDO RETROSPECTIVO E MULTICÊNTRICO COLABORATIVO

## CLINICAL AND RADIOLOGICAL EVALUATION OF PATIENTS AFFECTED BY FLORID OSSEOUS DYSPLASIA – A MULTICENTER COLLABORATIVE AND RETROSPECTIVE STUDY

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Dissertação apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Mestra em Estomatopatologia, na Área de Patologia.

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Orientador: Prof. Dr. Pablo Agustin Vargas

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A Ata da defesa com as respectivas assinaturas dos membros encontra-se no processo de vida acadêmica do aluno.

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*Se você quer ir longe, vá acompanhado"*

- Provérbio africano

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## RESUMO

A displasia óssea florida (DOF) é uma doença fibro-óssea benigna caracterizada pela substituição gradual de osso normal por tecido conjuntivo fibroso e/ou massas cementoides e afeta principalmente mulheres negras. O diagnóstico é baseado nos aspectos clínicos e radiográficos e o tratamento geralmente é conservador. O objetivo desse trabalho é avaliar as principais características clínicas e radiográficas de uma série de casos diagnosticados como DOF provenientes de quatro países. Um total de 82 casos foram incluídos no estudo, provenientes dos países: Brasil (n=40), Guatemala (n=3), Estados Unidos (n=13) e África do Sul (n=26). O gênero feminino representou 98,8% da amostra, com uma média de idade de 53,9 anos e 77,4% sendo melanodermas. A distribuição por cor da pele apresentou diferença entre os países, sendo 100% da amostra nos EUA, 84,6% entre os sul africanos e 66,6% dos brasileiros de cor negra. As lesões foram mais frequentes em mandíbula (100% dos casos) e foram classificadas como precoces em 2,4% dos casos, intermediárias em 41,4% e avançadas em 56,1%. Os estágios da doença foram diretamente correlacionados com a idade e o diagnóstico foi realizado mais frequentemente em estágios e idades mais avançadas. A menor proporção de pacientes negros no Brasil pode ser devido à importante miscigenação presente nesse país, contrastando com os outros dois países em análise (África do Sul e EUA). A avaliação através da radiografia panorâmica apresentou divergências na maxila e região anterior de mandíbula, devendo ser questionado como o melhor método para o diagnóstico dessa lesão.



**Palavras-chave:** Lesões fibro-ósseas, displasia óssea florida, etnia, estudo multicêntrico, radiografia panorâmica.

## ABSTRACT

Florid osseous dysplasia (FOD) is a fibro-osseous disease characterized by multifocal gradual substitution of normal bone by fibrous connective tissue and/or cementum-like masses that mainly affects Black women. Diagnosis is based on clinical and radiological aspects and treatment is usually conservative. The aim of this study is to evaluate the main clinical and radiological features of FOD diagnosed in a series of patients retrieved from four different countries. A total of 82 patients diagnosed with FOD from Brazil (n=40), Guatemala (n=3) United States of America (n=13) and South Africa (n=26) were selected. Females represented 98.8% of the sample, mean age of the patients was 53.9 years and 77.4% were Black. Distribution of ethnicity/skin color was different among countries, with 100%, 84.6% and 66.6% of cases from USA, South Africa and Brazil, respectively, affecting Black patients. FOD mostly affected mandible and the lesions were radiologically classified as early (2.44%), intermediate (41.46%) and advanced (56.1%). The stage of the disease was directly correlated with age of the patients and the diagnosis is usually done in advanced ages, in stages with more obvious radiopacity. The frequent racial miscegenation seen in Brazil seems to be the reason for the difference in ethnical distribution comparing to the other two countries (South Africa and USA).The assessment through panoramic radiography showed divergences rates in the maxilla and the anterior mandible, which might indicate that this method is not suitable to diagnose this disease.



**Keywords:** fibro-osseous lesions, florid osseous dysplasia, ethnicities, multicenter study, panoramic radiography.

**SUMÁRIO**

## 1. INTRODUÇÃO

Lesões fibro-ósseas benignas (LFOB) compreendem um grupo de proliferações reativas, displásicas e neoplásicas que incluem displasia fibrosa, fibroma ossificante e displasia óssea (Noffke et al, 2012; Netto et al, 2013). Esse grupo de lesões compartilha de aspectos histopatológicos muito similares e apresentam alguns aspectos clínicos e radiográficos específicos (Speight, Carlos, 2006, MacDonald, 2015). LFOB são caracterizadas por substituição do osso normal por tecido conjuntivo fibroso com deposição gradual de osso imaturo que gera uma característica radiográfica que varia de uma imagem completamente radiolúcida até completamente radiopaca nos ossos mandibulares (Kawai et al, 1999).

De acordo com a classificação estabelecida pela Organização Mundial de Saúde (OMS) em 2005, os três tipos de LFOB incluem as displasias fibrosas, as displasias ósseas e os fibromas ossificantes e podem ser subclassificados em: displasia fibrosa monostótica, displasia fibrosa poliostótica e displasia fibrosa craniofacial; displasia óssea periapical, displasia óssea focal, displasia óssea florida e cementoma gigantiforme familiar; fibroma ossificante, fibroma ossificante trabecular juvenil e fibroma ossificante psamomatoide juvenil (Barnes et al, 2005).

O diagnóstico correto e preciso do tipo de LFOB pode ser desafiador e requer associação clínica (normalmente a localização da lesão, idade, gênero e histórico genético do paciente), radiográfica (tipo de imagem, limites e localizações de acometimento) e de achados histopatológicos (quando indicado). Um dos maiores desafios de diferenciação diagnóstica é entre o fibroma ossificante e as displasias fibrosas e displasias ósseas focais. Resumidamente, o fibroma ossificante é considerado uma neoplasia benigna verdadeira com predileção pela região posterior da mandíbula e é caracterizada por imagem radiográfica variando de radiolúcida a radiopaca bem delimitada, normalmente associada a aumento de volume ósseo na área afetada. A displasia fibrosa apresenta predileção pela maxila e possui uma aparência radiográfica mal definida semelhante a vidro despolido. A displasia óssea focal, assim como as outras displasias ósseas, afeta regiões de periodonto, mais frequentemente em região posterior de mandíbula, raramente apresentando aumento de volume local (Su et al, 1997; Eversole et al, 2008).

O aspecto histopatológico dessas lesões apresenta um estroma hipercelularizado, rico em fibroblastos, podendo ser mais colagenizado algumas vezes. O componente ósseo é caracterizado por neoformações ósseas em aspecto

ondulado ou trabéculas irregulares (Eversole et al, 2008). Em alguns casos, é impossível distinguir histologicamente as variantes de lesões fibro-ósseas benignas, tornando mandatória a correlação clínica e imagenológica nesses casos para a liberação do laudo pelo patologista oral (Waldron, 1999; Alsufyani, Lam, 2011).

## 1.1 DISPLASIA ÓSSEA

Displasias ósseas (DO) compõem um grupo de desordens que afetam principalmente os maxilares em regiões dentadas ou edêntulas do processo alveolar e tem sua origem nos tecidos do ligamento periodontal. (Kawai et al, 1999; Slootweg, 2005; Alsufyani, Lam, 2011). Esse grupo é subdividido em três variantes (displasia óssea focal, periapical e florida), mas alguns autores consideram o cementoma gigantiforme familiar (uma doença similar à displasia óssea florida, mas com características clínicas e genéticas específicas) parte desse conjunto (Slootweg, 2005; Speight, Carlos, 2006; MacDonald, 2015). Essas condições compartilham de algumas características clínicas, histopatológicas e radiográficas semelhantes, exceto pela localização e grau de acometimento das lesões nos maxilares. A displasia óssea focal (DOFoc) é uma alteração isolada e circunscrita que afeta mais frequentemente as regiões de periodonto na região posterior de mandíbula, apresentando várias similaridades com o fibroma ossificante (Bhandari et al, 2012). A displasia óssea periapical (DOP) em geral tem apresentação multifocal, porém restrita a regiões de suporte ósseo em anterior de mandíbula, raramente excedendo 1cm de diâmetro cada lesão. A displasia óssea florida (DOF) é extensa e multifocal, geralmente com envolvimento dos quatro quadrantes dos ossos maxilares (Speight, Carlos, 2006; MacDonald, 2015).

Radiograficamente, as DO, inicialmente nos estágios precoces, apresentam imagem radiolúcida bem definida em proximidade com os ápices dentários e frequentemente induzem o diagnóstico equivocado de lesões periapicais inflamatórias. Subsequentemente, devido ao processo de calcificação progressiva, o estágio intermediário apresenta uma imagem mista radiolúcida e radiopaca com halo radiolúcido bem demarcado. Por fim, o estágio tardio apresenta uma imagem radiopaca difusa e mal definida (Eversole et al, 2008). Histopatologicamente, as características também são divididas em três estágios: precoce, intermediário e tardio. O estágio precoce é caracterizado por estroma vascular fibroso associado a trabéculas ósseas dispersas. No estágio intermediário, observa-se várias trabéculas

osteoides com modificações na fibrose do estroma e surgimento de calcificações semelhantes a cemento. O estágio tardio apresenta um osso trabecular curvilíneo denso associado a estroma menos fibroso e difusas massas semelhantes a cemento (Eversole et al, 2008). Eventualmente, alguns perfis inflamatórios ou contaminações secundárias (como infecção por *Actinomyces*) podem ser vistos associados (Smith et al, 2011).

As DO, exceto o cementoma gigantiforme familiar, afetam principalmente mulheres negras de meia-idade. Como mostrado previamente, cerca de 5,5% das mulheres negras possuem algum grau de displasia óssea observada em radiografias (Neville, Albenesius, 1986). Apesar da clara predileção por afrodescendentes, essa alteração também pode ser observada em caucasianos e asiáticos (Kim et al, 2011). A média de idade dos pacientes afetados pelas DO é em torno da quinta e sexta décadas de vida. No entanto, um estudo no Japão mostrou de forma interessante que a média de idade dos indivíduos do gênero masculino afetados pela doença era maior do que a média de idade das mulheres afetadas, o que suporta a hipótese de que as influências no remodelamento ósseo nas DO podem ser, pelo menos parcialmente, associadas ao equilíbrio hormonal (Kawai et al, 1999).

Estudos sobre a frequência de DO na América do Sul ainda são muito escassos e a influência étnica nessa população ainda não é bem esclarecida. Diferente de uma revisão sistemática que mostra uma prevalência de 3% de caucasianos em pacientes com DO (MacDonald-Jankowski, 2003), Netto et al (2013) mostraram que cerca de 21% dos pacientes com DO eram caucasianos em uma amostra de LFOB do Rio de Janeiro, Brasil. Além disso, a DOF foi a lesão mais comum entre todas as LFOB nessa amostra (Netto et al, 2013), provavelmente devido ao fato de os autores terem incluído todos os casos de LFOB, inclusive aqueles diagnosticados apenas clínica e radiograficamente. Portanto, estudos mais completos com diferentes etnias são necessários para esclarecer essa prevalência.

## 1.2. DISPLASIA ÓSSEA FLORIDA

Primeiro descrita por Melrose, Abrams e Mills em 1976, a DOF é a forma mais exuberante das DO (Worawongvasu, Songkampol, 2010; Kose et al, 2013). Em geral, afeta a região posterior de mandíbula, apesar de também ser encontrada em maxila, com frequente apresentação bilateral e simétrica, envolvendo os quatro quadrantes (Speight, Carlos, 2006; Glascoe et al, 2011; MacDonald, 2015).

O aspecto radiográfico apresenta imagens de massas multifocais radiolúcidas, mistas ou radiopacas envolvendo os ápices das raízes dos dentes. Essas massas tendem a crescer e se tornar predominantemente radiopacas (Sarmento et al, 2013). Em comparação com DOP e DOFoc, a DOF apresenta significantemente maior radiopacidade (Alsufyani, Lam, 2011). Importante destacar que, no estágio precoce, o aspecto radiográfico pode mimetizar uma lesão periapical, portanto, deve-se estar atento a vitalidade dental e levar em consideração a DOF no diagnóstico diferencial para evitar tratamentos endodônticos desnecessários (Huh, Shin, 2013).

Geralmente, o diagnóstico de DOF é realizado como achado radiográfico de rotina, sendo baseado somente em correlação dos aspectos clínicos e radiográficos sem a necessidade de tratamento, na maioria dos casos (Das et al, 2013, MacDonald, 2015; Alsufyiani, Lam, 2011). Ocasionalmente, os pacientes podem apresentar sintomatologia devido a infecções nos tecidos ósseos acometidos pela doença e, nesses casos, o tratamento é normalmente baseado em antibioticoterapia combinada ou não com debridamento e remoção do osso afetado. Devido à vascularização deficiente nas regiões de DOF no estágio tardio, o risco de infecções, formação de sequestro ósseo e osteomielite aumenta e, portanto, manipulações ósseas eletivas, como biópsias e extrações dentárias, devem ser evitadas ou, se indispensáveis, cuidadosamente planejadas (Kutluay Köklü et al, 2013; Kose et al, 2013). Além disso, é essencial que os cirurgiões-dentistas reforcem a higiene oral adequada aos pacientes afetados por DOF, incluindo visitas frequentes ao Periodontista para profilaxia, e radiografias panorâmicas periódicas para acompanhamento e prevenção de intervenções cirúrgicas (Waldron, 2009).

O cementoma gigantiforme familiar (CGF), igualmente encontrado em região posterior de mandíbula, é um importante diagnóstico diferencial de DOF. Um critério muito relevante para diferenciar essas duas entidades é o padrão de dominância autossômica encontrada no CGF, permitindo que seja observado o mesmo padrão da doença em crianças e adolescentes, afetando ainda uma proporção maior de pacientes caucasianos e do gênero masculino na mesma família. Essa doença mostra um perfil mais agressivo de crescimento progressivo e exuberante, produzindo deformidades faciais, que geralmente requerem intervenções cirúrgicas para controle da doença. (MacDonald-Jankowski, 1992; MacDonald-Jankowski, 2003). Um caso publicado recentemente por Srivastava et al. (2012) considerou uma

displasia óssea florida familiar, contudo, o paciente afetado era jovem, do gênero masculino e com membros da família também afetados pela doença, tornando necessária a exclusão de CGF no diagnóstico diferencial.

O diagnóstico diferencial torna-se importante ainda em relação à Doença de Paget que, ao contrário da DOF, normalmente afeta tanto corpo quanto ramo de mandíbula e observa-se perda da lâmina dura do osso alveolar. Além disso, ocorre deformidade em vários ossos do corpo, aumento dos níveis séricos de fosfatase alcalina e o paciente geralmente apresenta dor e distúrbios neurológicos (Pitak-Arnnop et al, 2009; Kutluay Köklü et al, 2013).

O cisto ósseo simples (cavidade óssea idiopática) pode apresentar-se associado à DOF. Considerado um pseudo-cisto que usualmente afeta os ossos maxilares de jovens nas duas primeiras décadas de vida, o cisto ósseo simples pode afetar mandíbula, maxila e ossos longos. Em geral, essas lesões são únicas, produzem imagem radiográfica radiolúcida bem definida e tem predileção pela região posterior de mandíbula. Alguns estudos comentam sobre a associação do cisto ósseo simples em adultos e idosos, predominantemente mulheres, com DOF (Mahomed et al, 2005; Chadwik et al, 2011), mas a real relação entre essas duas alterações ainda não é bem estabelecida. Alguns estudos sugerem que, como a cavidade surge em uma área de DOF pré-existente, o desenvolvimento da displasia óssea pode causar interrupção do fluxo normal de drenagem intersticial, levando ao acúmulo de fluidos e consequente reabsorção óssea (Wakasa et al, 2002).

Além disso, o osteossarcoma é uma neoplasia óssea maligna que deve ser considerada como uma possível complicação da DOF. Apesar de ser uma condição rara, pode se desenvolver a partir de uma DOF pré-existente, tornando o diagnóstico ainda mais desafiador e chamando atenção para a importância do acompanhamento clínico-radiográfico regular dos pacientes nessa condição (Lopes et al, 2010).

Apesar de a DOF ser uma doença conhecida em várias partes do mundo, não existem estudos multicêntricos internacionais correlacionando suas principais características. O objetivo desse trabalho é avaliar características clínicas e radiográficas de uma série de casos diagnosticados como DOF provenientes de quatro países, considerando a apresentação clínica da doença, seu comportamento biológico e comparando os níveis de concordância entre avaliadores no diagnóstico radiográfico da lesão.

## 2. ARTIGO: CLINICAL, DEMOGRAPHIC AND RADIOGRAPHIC ANALYSIS OF 82 PATIENTS AFFECTED BY FLORID OSSEOUS DYSPLASIA: AN INTERNATIONAL COLLABORATIVE STUDY

Artigo submetido ao periódico Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology (Anexo 2)

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**Abstract**

**Objective.** The aim of this study was to correlate clinical, demographic and radiographic aspects of 82 cases of Florid Osseous Dysplasia (FOD) from four different countries assessed by five different reviewers.

**Study design.** Retrospective data of patients diagnosed with FOD were obtained from archives of five different Institutes and analyzed according to clinical and radiographic criteria.

**Results.** A total of 82 cases of FOD were included in the study. The majority (77.5%) of FOD cases affected Black women. The disease mainly affected the mandible (100%) and the stage of the lesion was directly correlated with the age ($p<0.05$). The rates of convergence showed confluence of assessment in the mandible (posterior) and the highest rate of divergence between the reviewers was assessing involvement in the maxilla. There were no differences among the characteristics of the lesion provided by the 5 Institutions, except for the variable proportion of Blacks affected by the disease.

**Conclusions.** FOD mostly affects the mandible of middle-age Black women and its stage is correlated with the age of the patients. Although panoramic radiography is used for diagnosis, the divergence in assessment of the maxilla might indicate that this method is not the most suitable to evaluate this area.

**Key-words:** florid osseous dysplasia, prevalence, panoramic radiograph, mandible, maxilla, multicentre study.

## Introduction

Osseous dysplasia (OD) represents a group of benign fibro-osseous lesions characterized by the replacement of the normal bone by fibrous connective tissue with immature bone deposition that gradually becomes sclerotic producing radiological features varying from a complete radiolucency to radiopacity. [1] It affects mainly Black women in the fifth to sixth decades of life, although it is also seen in Caucasians and Asians. [2-4]

This group is subdivided into three variants called focal, periapical, and florid OD, which affects mainly the jaws in the tooth-bearing or edentulous alveolar ridges. There is some evidence that OD arises from cells in the periodontal ligament tissue. [1,5,6] These three variants share some similar clinical, histopathological and radiographic features, except for location of the lesions and extension of maxillary involvement with periapical OD occurring in the anterior mandible, focal OD in islolated areas except in the anterior mandible and florid OD multifocally, often in both the mandible and maxilla. [5,7,8]

First described by Melrose et al in 1976,[9] florid osseous dysplasia (FOD) is the most exuberant variant of OD.[10,11] It commonly affects the posterior mandible, although it can also be encountered in the maxilla and often presents a bilateral and as a symmetrical pattern involving all four quadrants. [7,12,13]

Radiographically, FOD shows multifocal confluent radiolucency, mixed or radiopaque images surrounding the teeth root apices. These images have a tendency to increase in size and to become predominantly radiopaque.[14] In the early stage, the radiographic appearance can mimic an inflammatory periapical lesion, therefore it is important to consider FOD in the differential diagnosis of periapical radiolucencies and be aware of tooth vitality, avoiding unnecessary endodontic treatment because teeth affected by FOD are vital.[15]

Due to the histological similarity of fibro-osseous lesions and the absence of swelling or symptoms, in general, FOD is diagnosed based solely on clinical and radiographic correlation and coincidentally on routine radiographic examinations.[6,16] Some differential diagnosis should include conditions such as familial gigantiform cementoma, the osteomas of Gardners Syndrome and Paget's disease of bone,

requiring other complementary exams and the clinician's consideration.[13,14,17] Additionally, some other lesions as simple bone cysts have been described occurring concomitantly with FOD [18,19] and, although rare, osteosarcoma can develop in association with a pre-existing FOD, making the differential diagnosis even more difficult and highlighting the importance of regular follow-up of the affected patients.[17]

Although FOD is a well-known entity in most parts of the world, there is no international multicenter study correlating the main characteristics of the disease. The aim of this study was to correlate clinical, demographic and radiographic aspects of 82 cases of FOD from four different countries assessed by 5 reviewers.

**Materials and Methods**

This study was based on retrospective data of patients diagnosed with FOD obtained from archives of five different Institutes [Orocentro, Piracicaba Dental School, Brazil (from 1992 to 2014); Laboratory of Oral Pathology, State University of Rio de Janeiro, Brazil (from 2005 to 2014); Division of Pathology, Head and Neck Clinical Center, Guatemala (from 1997 to 2011); Department of Oral Pathology and Oral Biology, University of Pretoria, South Africa (from 2012 to 2014); The Texas A&M University Baylor College of Dentistry, United States of America (from 2003 to 2014)]. The Ethics Committee in Research of the Piracicaba Dental School approved the current study (Protocol number: 043/14).

Five reviewers assessed 122 cases diagnosed as FOD using panoramic radiographs. The radiographic features analyzed included: affected sextant (right, central and left maxilla; right, central and left mandible); stage of the lesion (early, intermediate or advanced); and number of teeth in the affected area. These criteria were correlated with clinical and demographic data (age, color of skin, gender, symptoms, treatment, infection, and swelling). The early stage was considered when the lesions in the periapical region were predominantly radiolucent, the intermediate stage were represented by mixed radiopaque/radiolucent images and the advanced stage should present a prominent radiopaque image. All radiographs and information reflected the time of diagnosis. Cases in which the quality of the exam was poor or at least one reviewer disagreed with the diagnosis were excluded from the study.

Statistical analyses were performed using the SAS system (SAS Institute Inc. 9.3. Cary:NC, 2010). Bivariate correlations were assessed by chi-square test and the correlation coefficient of Spearman. The analysis of variance between the five reviewers was established by Tukey's test. Interexaminer agreements were assessed using Cohen's Kappa test to analyze the reliability of the examiners and the agreement was considered fair when Kappa was between 0,20-0,40, moderate if Kappa was between 0,40-0,60 and substantial when Kappa was between 0,60-0,80.[20]

## Results

Among 122 available FOD cases, 60 were from Brazil (Rio de Janeiro and Piracicaba), 4 from Guatemala (Guatemala City), 23 from USA (Dallas) and 30 from South Africa (Pretoria). After the 5 reviewers analyzed all panoramic radiographs, 40 cases were excluded from the sample because of lack of quality of the radiography or disagreement with the diagnosis. The final sample consisted of 40 cases from Brazil, 3 from Guatemala, 13 from USA, and 26 from South Africa. The mean age was 53.9 years (27-79 years) and 98.8% were women. Blacks represented 77.5% of the sample, although this proportion differed significantly when separated by country ($p<0.05$). Demographic and clinical data are summarized in Table 1.

**Table 1.** Demographic and clinical data of 82 patients diagnosed with FOD.

| | **Brazil (n=40)** | **Guatemala (n=3)** | **United States (n=13)** | **South Africa (n=26)** | **Total** | **p** |
|---|---|---|---|---|---|---|
| **Mean age (years)** | 55.6 | 45 | 53 | 52.9 | 53.9 (27 – 79) | |
| **Gender (n=82)** | | | | | | |
| Male | 0 | 0 | 0 | 1 (3.8%) | 1 (1.2%) | 0.0001* |
| Female | 40 (100%) | 3 (100%) | 13 (100%) | 25 (96.2%) | 81 (98.8%) | |
| **Skin color (n=71)** | | | | | | |
| Black | 24 (66.7%) | NA | 9 (100%) | 22 (84.6%) | 55 (77.5%) | 0.022* |
| Non-black | 12 (33.3%) | NA | 0 (0%) | 4 (15.4%) | 16 (22.5%) | |
| **Infection (n=50)** | | | | | | |
| Yes | 15 (40.5%) | NA | 3 (23.1%) | NA | 18 (36%) | 0.047* |
| No | 22 (59.5%) | NA | 10 (71.9%) | NA | 32 (64%) | |
| **Symptoms (n=51)** | | | | | | |
| Yes | 26 (70.3%) | 1 (100%) | 3 (23.1%) | NA | 30 (58.8%) | 0.207 |
| No | 11 (29.7%) | 0 | 10(71.9%) | NA | 21 (41.2%) | |
| **Swelling (n=52)** | | | | | | |
| Yes | 18 (46.2%) | NA | 4 (30.8%) | NA | 22 (42.3%) | 0.267 |
| No | 21 (53.8%) | NA | 9 (69.2%) | NA | 30 (57.7%) | |

*$p<0.05$; NA = Not Available

Clinical data showed the presence of infection in 36% out of 50 cases for which this information was available. However, this proportion varied significantly between Brazil and United States ($p<0.05$). Regarding the chief complaint at the first appointment, 58.8% (n=51) and 42.3% (n=52) of patients claimed symptoms and swelling, respectively (Table 1). Nevertheless, only 16 patients (31.4%; n=51) received some type of treatment, such as antibiotics, surgery or sequestrectomy ($p<0.01$). Additionally, 92.9% of treated patients were symptomatic ($p<0.01$) (Table 2).

In spite of the absence of significant correlation, the results also showed that as the age of patients increased, the percentage of patients complaining about symptoms increased (Table 2). The stage of the disease showed 2 cases in the early stage (2.4%), 34 in the intermediate stage (41.5%) and 46 in the advanced stage (56.1%) (Figures 1A, 1B and 1C, respectively). The increase in age also showed correlation with more advanced stages, being considered positive and significant ($p<0.05$); however, it was negative when comparing stage with the number of teeth in the affected area (Figure 2A and B, respectively).

The interexaminer agreements applied to the assessment of stage of the disease were considered moderate or substantial in most combinations, varying from 41.8% to 78.3%. The analysis showed fair agreement in only two cases, represented by Kappa values of 29.2% and 34.4% (Table 3).

The analysis of divergence between the examiners opinion´s on the presence of FOD involvement showed lower rates in the posterior region of the mandible compared to the maxilla and the anterior mandible ($p<0.05$) (Figure 3A). The convergence analysis demonstrated greater agreement between the examiners in the posterior mandible (Figure 3B). The mandible was affected in all cases and the maxilla was involved in 43 out of 82 cases (52.4%) (Figure 4).

**Table 2.** Chi-square test for symptom-age and symptom-treatment.

| | **Symptom** | | |
|---|---|---|---|
| | **No** | **Yes** | **p** |
| **Age range (years)** | | | |
| 27-40 | 4 (80%) | 1 (20%) | 0.128 |
| 40-50 | 8 (50%) | 8 (50%) | |
| 50-60 | 5 (35.7%) | 9 (64.3%) | |
| 60-79 | 4 (25%) | 12 (75%) | |
| **Treatment** | | | |
| No | 20 (57.1%) | 15 (42.9%) | 0.0006* |
| Yes | 1 (7.1%) | 13 (92.9%) | |

*p<0.05

**Table 3.** Interexaminer agreements for evolutive stage (early, intermediate and advanced).

| | ***Kappa*** | ***95% Confident Interval*** | |
|---|---|---|---|
| ***Examiners*** | | ***Lower*** | ***Upper*** |
| **1 – 2** | 0.7825 | 0.6598 | 0.9052 |
| **1 – 3** | 0.7212 | 0.5818 | 0.8607 |
| **1 – 4** | 0.4180 | 0.2596 | 0.5763 |
| **1 – 5** | 0.6935 | 0.5523 | 0.8348 |
| **2 – 3** | 0.5891 | 0.4375 | 0.7408 |
| **2 – 4** | 0.3438* | 0.2042 | 0.4835 |
| **2 – 5** | 0.6726 | 0.5163 | 0.8288 |
| **3 – 4** | 0.4336 | 0.2739 | 0.5933 |
| **3 – 5** | 0.5874 | 0.4398 | 0.7350 |
| **4 – 5** | 0.2918* | 0.1613 | 0.4223 |

* Fair agreement rate

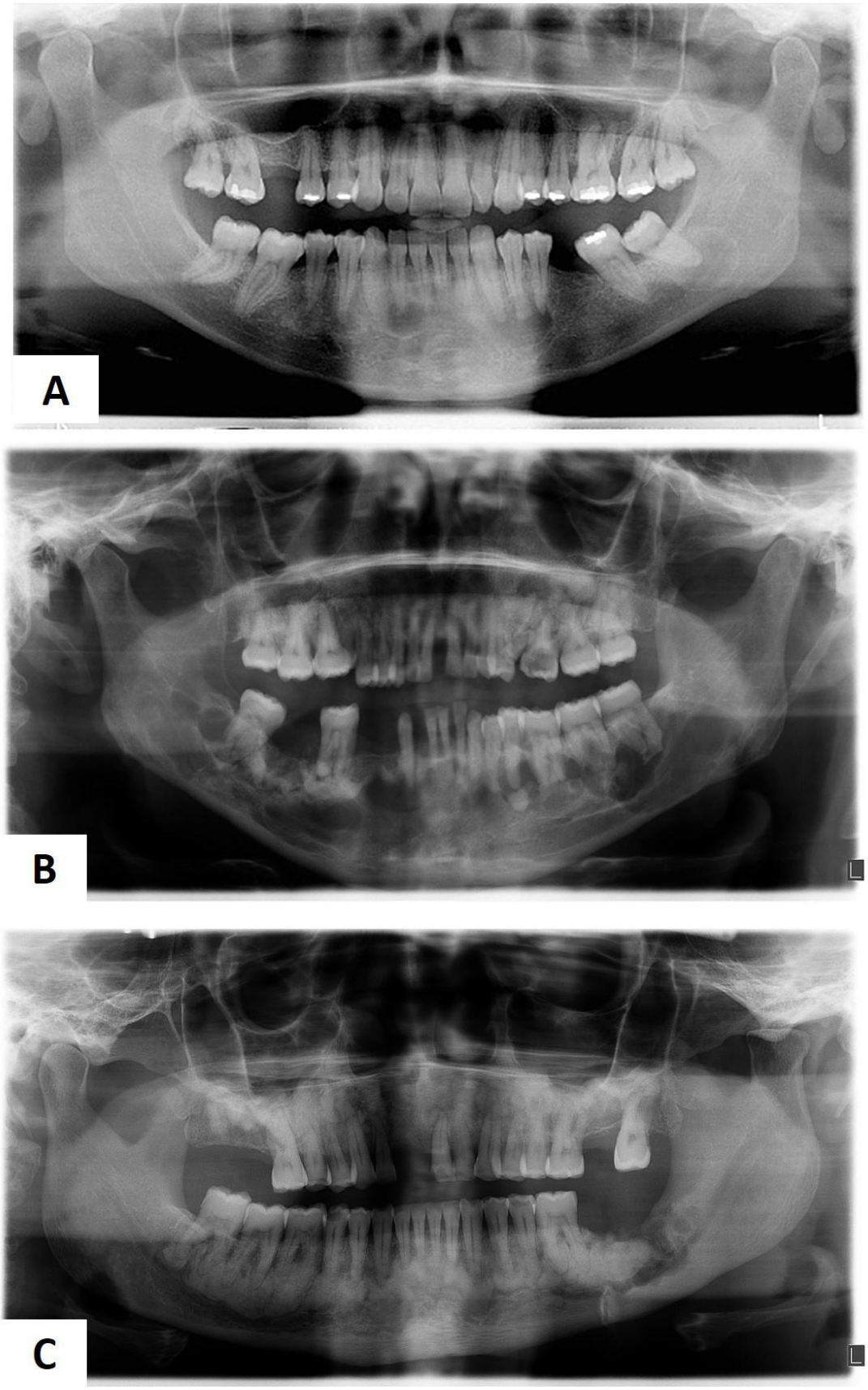


**Figure 1.** Representative radiographies of three stages of FOD. Early (A), intermediate (B) and advanced (C) stages.

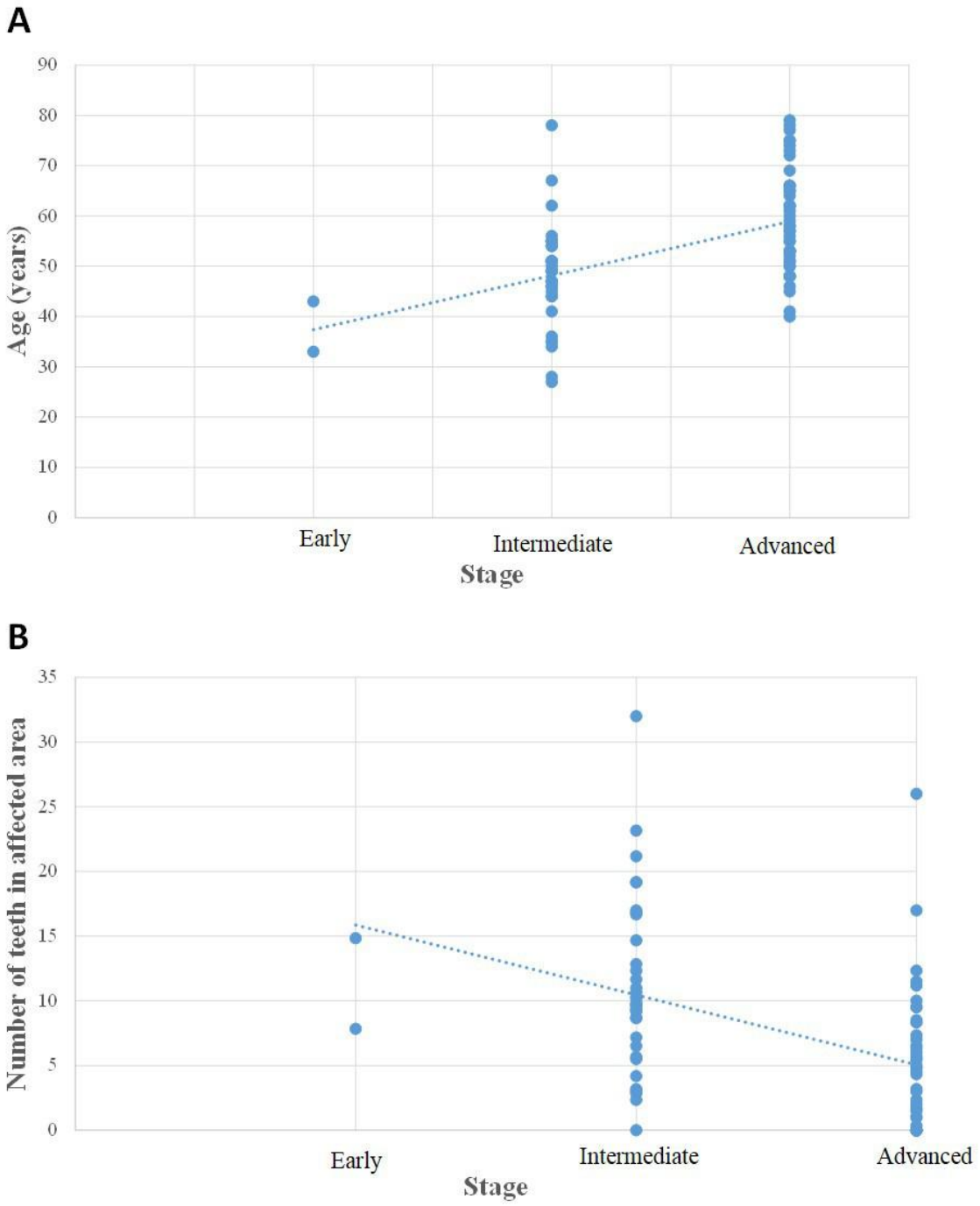


**Figure 2.** Distribution of stage by age (A) and number of teeth in affected area (B). Stage 1 = Early; Stage 2 = Intermediate; Stage 3 = Advanced.

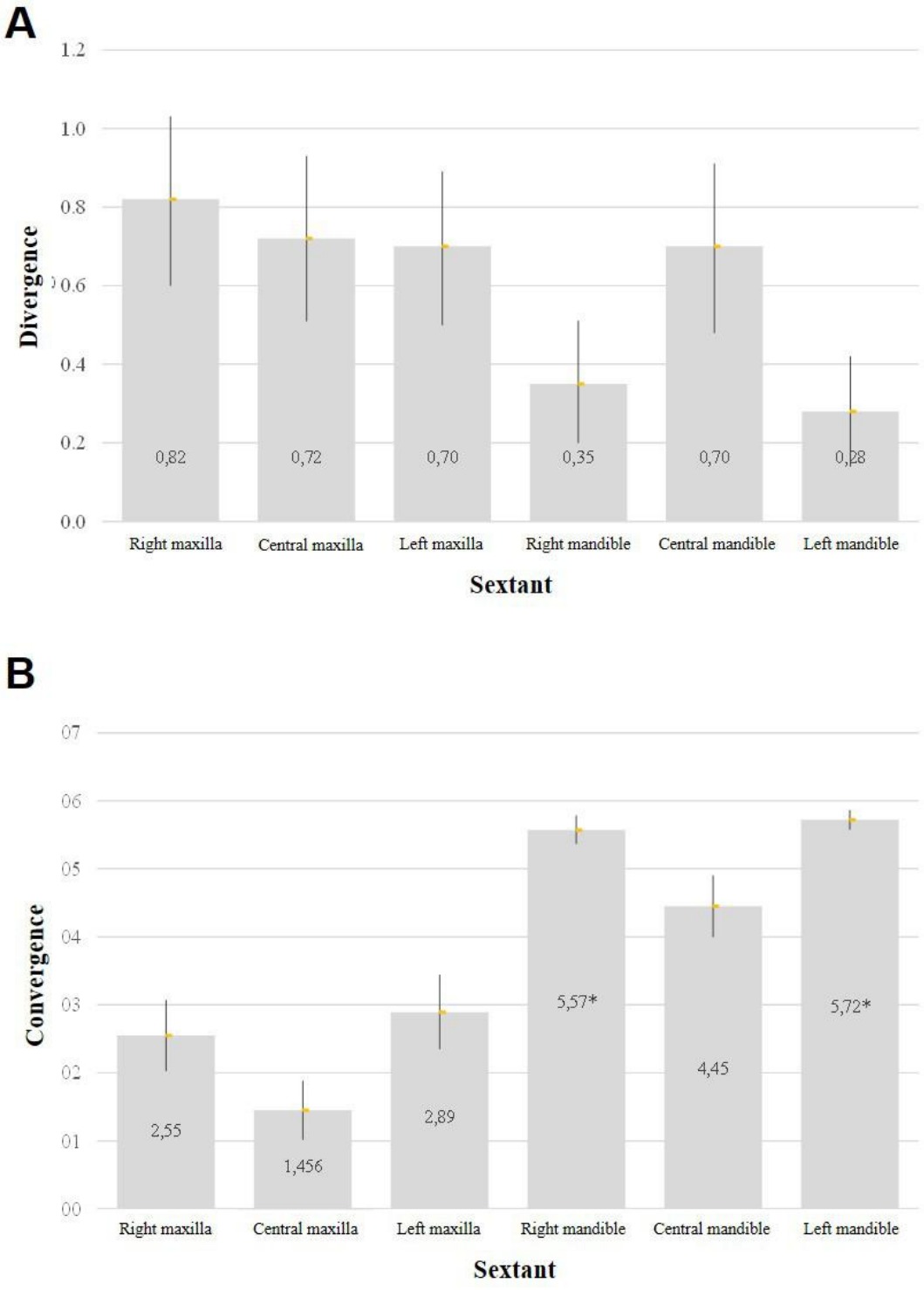


**Figure 3.** Affected sextants. Divergence of agreement (A). Convergence agreement (B). *p<0.05

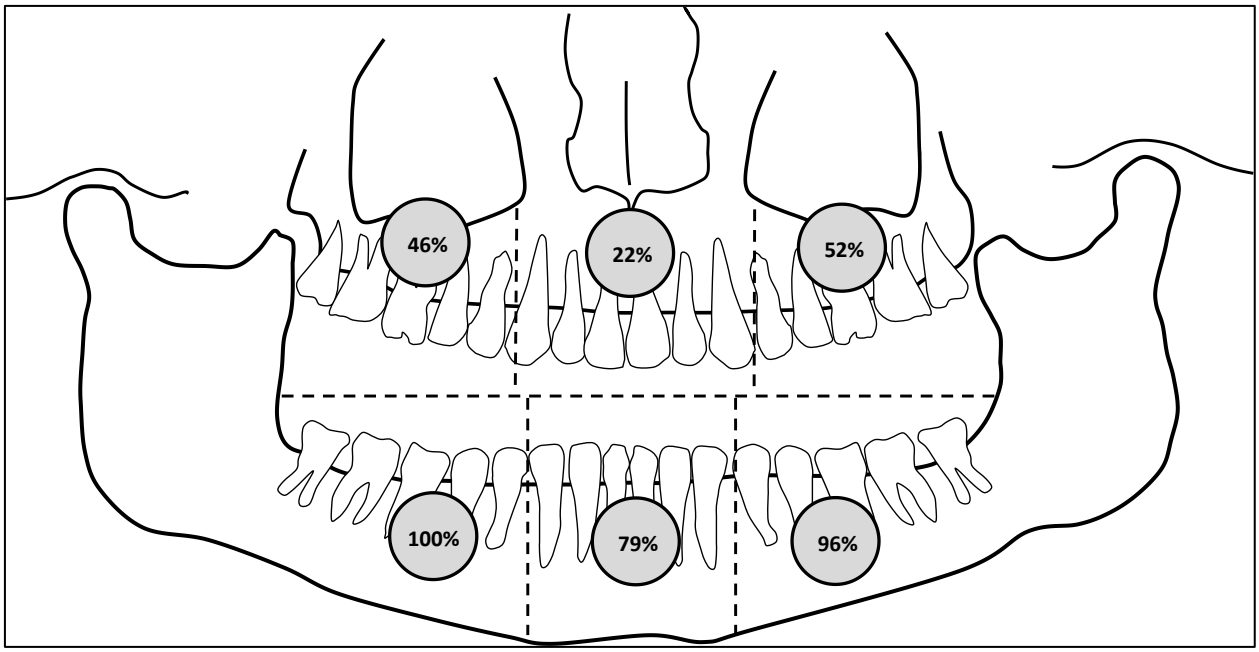


**Figure 4.** Distribution of the frequency of FOD lesions by sextant.

## Discussion

FOD is a well-known entity characterized by replacement of healthy bone by sclerotic bone.[7,8] The diagnosis is mainly based on clinical and radiographic aspects, because their histologic features are similar to other fibro-osseous lesions.[6,21] In general, the condition presents no obvious signs and symptoms and the diagnosis is established in middle-aged Black women as an incidental finding on panoramic radiographs.[13] The present study evaluated 82 cases diagnosed as FOD and showed a prevalence of 98.8% for women, which is in accordance with published evidence.[4] The mean age at diagnosis found in this study was 56 years, but varied from 27 to 79 years, similar to previous findings.[4] The main cause remains unknown, but some genetic or hormonal influences have been suggested;[8] therefore, further studies are necessary to clarify this correlation.

In an extensive systematic review including 158 cases of FOD from 17 series, MacDonald-Jankowski[4] showed that 59% were Black, 37% Oriental, and 3% Caucasian. On the other hand, the present study reported a rate of 77% of Black people, but it varied according to the country. Brazil was the country with more miscegenation, presenting a rate of 66.7% of Blacks, in contrast with the USA and

South Africa where Blacks were affected at rates of 100% and 84.6%, respectively. Curiously, except for South Africa, the Southeast and South regions in Brazil and the entire USA have a great presence of Oriental descendants, but this study did not show any case in this specific subgroup.

In general, FOD is an indolent disease discovered accidentally in routine radiography. Occasionally, patients can present with symptoms such as pain or swelling and purulent discharge due to infection in the affected bone; treatment of these specific cases is usually antibiotic therapy with or without surgical debridement and removal of the affected bone. Given the poor vascularization of the mature FOD lesions, the risk of infection, sequestrum formation and osteomyelitis increases, therefore elective bone manipulations, such as biopsies and teeth extractions, should be avoided or (when necessary), carefully planned.[11,22] In this research, 18 out of 50 patients presented with infection, 30 out of 51 patients had symptoms and among the 52 patients, 22 presented with swelling at the time of clinical exam. It is important to mention that only 16 patients received some type of treatment and from those, only one case was asymptomatic, which reinforces the concept that interventions in FOD should be reserved only when really necessary.

Comparing the two studies of MacDonald-Jankowski, the study including 17 cases of FOD diagnosed by histological patterns showed the mean age was higher (62,1 years) than in the study of 16 cases diagnosed only by clinical and radiographic features (52,1 years).[23,24] This difference might be explained by the evolution of the disease, because, as shown in the present data, the stage of the disease is directly correlated with age and as the age increases, more patients become symptomatic which might necessitate antibiotics and surgical intervention. Also important, the relation between age and the number of teeth showed to be inversely proportional, which means that the absence of teeth in areas affected by OD might contribute to bone resorption and as the bone affected by OD is dense and poorly vascularized, absence of teeth, masticatory forces and prosthesis trauma might facilitate bone exposure and, consequently, the development of infection and symptoms. However, affected areas with teeth should also be considered suitable to infections because of possibilities of periodontal disease, periapical lesions or tooth extraction.

Radiographically, FOD can present initially as a totally radiolucent lesion, which characterizes the earlier stage of the lesion, before changing to a mixed radiolucent and radiopaque appearance, called intermediate stage, and finally becoming entirely radiopaque, reaching the advanced phase of the disease.[5,21] Most cases (97.7%) included in the present study were diagnosed as either being of the intermediate or advanced stages. This feature could be associated with the fact that the diagnosis is achieved when patients seek conventional dental treatment and need a panoramic radiography for the planning or related to the difficulty to identify radiolucent lesions as a characteristic FOD. Additionally, symptoms tend to occur in intermediate and advanced stages, which might contribute to the patient look for treatment, being diagnosed at these stages.

In 2011, Alsufyani and Lam emphasized importance to make the correct diagnosis of osseous lesions.[6] Their study counted on standardized imaging exams and showed that the agreement for the diagnosis of OD between maxillofacial radiologists was substantial (80%-84%), while the agreement between general dentists was slight to moderate (13%-58%).[6] In the present study, the interexaminer agreement assessed by Kappa coefficient was considered moderate or substantial for this criterion in most of the combinations (41.8- 78.3%); therefore, the analysis was satisfactory, mainly considering that the radiographs came from different Institutes and presented varied types of quality which might interfere in the analysis.

Although FOD can affect any tooth-bearing area, it is more common in the mandible, symmetrically.[13] MacDonald-Jankowski showed in his systematic review in 2003 that 100% of cases affect the mandible and a lower rate (61.4%) affect the maxilla, consistent with our results, in which all cases affected the mandible and about half of the cases presented with lesion(s) in the maxilla (52.4%).[4] Moreover, the prevalence of sextant affected seems to be higher in the posterior regions, especially in the mandible. The divergence analysis demonstrated high rates in all the maxilla and the anterior mandible which might be explained by the difficulties in the assessment of these regions because of the superimposition of the overlying anatomic structures.

The panoramic radiographs are considered a satisfactory imaging modality for diagnosing most cases of FOD. In some challenging and indistinguishable cases, it

might be necessary to use additional imaging modalities such as periapical radiography, computed tomography and cone-beam computed tomography.[13] Forty cases were excluded from the present sample because of the differences in the diagnosis given by the examiners. The reasons included difficulty to distinguish some areas of involvement suggesting the differential diagnosis of focal osseous dysplasia and disagreement if some radiopaque lesions truly represented areas of OD.

Although the biopsy is a procedure that should be avoided in cases of FOD because of the increased of the risk of infection,[11] some cases require pathologic confirmation due to aggressive behaviour. One out of 82 cases presented with a large painful growth in the mandible that was biopsied and diagnosed as osteosarcoma.[17] In this specific case, the biopsy was crucial to confirm the possibility of malignant transformation of this benign disease. While only a few cases are described in the literature showing malignant tumor developing in association with FOD, it is important to be aware and maintain a rigorous follow-up of all these patients. [17,25,26]

In summary, FOD is a gradually progressive disease that affects mostly Black women worldwide and its evolution is directly correlated with the age of the patient. Accordingly, the disease followed the same pattern among different countries, except for the variable distribution of ethnicity. Due to high levels of divergence in the assessment of some difficult areas, such as the maxilla, the panoramic radiographic exam should be complemented with other accurate exams. It is recommended to leave surgical procedures exclusively to symptomatic cases. Dentists should stress the importance of adequate oral hygiene to patients affected by FOD, including frequent periodontal appointments and prophylaxis, and periodic radiographic follow-up because of the risk of developing other conditions as simple bone cyst and osteosarcoma.

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## 3. CONCLUSÃO

Os resultados apresentados permitem concluir que:

- A DOF é uma doença com alta predileção por mulheres e predomínio de melanodermas;
- O diagnóstico é estabelecido mais frequentemente nas fases intermediária e avançada da doença e em idade média de 53 anos, uma vez que a idade está diretamente correlacionada com a fase da doença;
- A doença afeta preferencialmente a mandíbula em região posterior;
- O alto grau de discordância entre os avaliadores na detecção da doença em radiografias panorâmicas na região da maxila permite sugerir que exames complementares (radiografias periapicais e tomografia computadorizada) devem ser considerados em todas as suspeitas de DOF, principalmente no esclarecimento de diagnósticos diferenciais e planejamentos terapêuticos;
- A inclusão de um caso raro de DOF associada a osteossarcoma chama a atenção para a importância do acompanhamento permanente desses pacientes, mesmo que essa seja uma doença fibro-óssea benigna de característica geralmente indolente;
- Não houve diferença no padrão geral de apresentação da doença entre os países estudados, exceto pela distribuição de pacientes melanodermas, que se apresenta significativamente variável dependendo da composição étnica do país estudado.

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## APÊNDICE 1

Tabela de dados demográficos, clínicos e radiográficos de 82 pacientes afetados por Displasia óssea florida.

| Caso | País de origem | Gênero | Idade | Cor da pele | Sintoma | Infecção | Tratamento | Estágio |
|---|---|---|---|---|---|---|---|---|
| 1 | Brasil | F | 51 | Melanoderma | NI | NI | Sim | 2 |
| 2 | Brasil | F | 43 | Melanoderma | Sim | Sim | NI | 1 |
| 3 | Brasil | F | 47 | Feoderma | NI | Sim | NI | 2 |
| 4 | Brasil | F | 65 | melanoderma | NI | NI | Sim | 3 |
| 5 | Brasil | F | 69 | Melanoderma | Sim | Sim | Sim | 3 |
| 6 | Brasil | F | 62 | Melanoderma | Sim | Sim | Sim | 2 |
| 7 | Brasil | F | 75 | Leucoderma | Sim | Sim | Sim | 3 |
| 8 | Brasil | F | 41 | Melanoderma | Sim | Não | Não | 2 |
| 9 | Brasil | F | 50 | Feoderma | Não | Não | Não | 3 |
| 10 | Brasil | F | 78 | Melanoderma | Sim | Sim | Sim | 2 |
| 11 | Brasil | F | 55 | Melanoderma | Sim | Não | Não | 2 |
| 12 | Brasil | F | 54 | Melanoderma | Sim | Não | Não | 2 |
| 13 | Brasil | F | 62 | Melanoderma | Sim | Sim | Sim | 3 |
| 14 | Brasil | F | 55 | Leucoderma | Sim | Não | Não | 2 |
| 15 | Brasil | F | 48 | NI | Sim | Não | Não | 3 |
| 16 | Brasil | F | 73 | Melanoderma | Sim | Sim | Não | 3 |
| 17 | Brasil | F | 66 | NI | Sim | Não | Não | 3 |
| 18 | Brasil | F | 51 | Melanoderma | Sim | Não | Não | 2 |
| 19 | Brasil | F | 62 | Melanoderma | Sim | Sim | Não | 3 |
| 20 | Brasil | F | 50 | Melanoderma | Sim | Sim | Não | 2 |
| 21 | Brasil | F | 41 | Feoderma | Não | Não | Não | 3 |
| 22 | Brasil | F | 75 | NI | Não | Não | Não | 3 |
| 23 | Brasil | F | 74 | Melanoderma | Não | Não | Não | 3 |
| 24 | Brasil | F | 53 | Leucoderma | Não | Não | Não | 3 |
| 25 | Brasil | F | 47 | Feoderma | Não | Não | Não | 2 |
| 26 | Brasil | F | 28 | Leucoderma | Não | Não | Não | 2 |
| 27 | Brasil | F | 46 | Feoderma | Não | Não | Não | 2 |
| 28 | Brasil | F | 78 | Melanoderma | Sim | Sim | Não | 3 |
| 29 | Brasil | F | 48 | NI | Sim | NI | NI | 3 |
| 30 | Brasil | F | 58 | Melanoderma | Sim | Sim | Sim | 3 |
| 31 | Brasil | F | 49 | Melanoderma | Não | Não | Não | 2 |
| 32 | Brasil | F | 27 | Melanoderma | Sim | Não | Não | 2 |
| 33 | Brasil | F | 49 | Melanoderma | Sim | Não | Não | 2 |
| 34 | Brasil | F | 44 | Melanoderma | Sim | Não | Não | 2 |
| 35 | Brasil | F | 58 | Melanoderma | Sim | Sim | Sim | 3 |
| 36 | Brasil | F | 59 | Leucoderma | Sim | Não | Sim | 3 |
| 37 | Brasil | F | 65 | Leucoderma | Sim | Sim | Sim | 3 |
| 38 | Brasil | F | 53 | Melanoderma | Sim | Sim | Sim | 3 |
| 39 | Brasil | F | 66 | Feoderma | Não | Não | Não | 3 |
| 40 | Brasil | F | 48 | Melanoderma | Não | Não | Não | 3 |
| 41 | EUA | F | 40 | Melanoderma | Não | Não | Não | 3 |
| 42 | EUA | F | 35 | NI | Não | Não | Não | 2 |
| 43 | EUA | F | 53 | Melanoderma | Sim | Sim | Sim | 3 |
| 44 | EUA | F | 54 | Melanoderma | Não | Não | Não | 2 |
| 45 | EUA | F | 45 | Melanoderma | Não | Não | Não | 3 |
| 46 | EUA | F | 79 | Melanoderma | Sim | Sim | Sim | 3 |
| 47 | EUA | F | 51 | Melanoderma | Não | Não | Não | 2 |
| 48 | EUA | F | 56 | NI | Não | Não | Não | 3 |
| 49 | EUA | F | 53 | NI | Não | Não | Não | 3 |
| 50 | EUA | F | 46 | Melanoderma | Não | Não | Não | 2 |
| 51 | EUA | F | 33 | NI | Não | Não | Não | 1 |
| 52 | EUA | F | 77 | Melanoderma | Sim | Não | Não | 3 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 53 | EUA | F | 67 | Melanoderma | Não | Sim | Sim | 2 |
| 54 | África do Sul | F | 51 | Melanoderma | NI | NI | NI | 2 |
| 55 | África do Sul | F | 47 | Melanoderma | NI | NI | NI | 2 |
| 56 | África do Sul | F | 60 | Melanoderma | NI | NI | NI | 3 |
| 57 | África do Sul | F | 61 | Melanoderma | NI | NI | NI | 3 |
| 58 | África do Sul | F | 48 | Melanoderma | NI | NI | NI | 3 |
| 59 | África do Sul | F | 55 | Melanoderma | NI | NI | NI | 2 |
| 60 | África do Sul | F | 57 | Melanoderma | NI | NI | NI | 3 |
| 61 | África do Sul | F | 55 | Melanoderma | NI | NI | NI | 3 |
| 62 | África do Sul | M | 56 | Melanoderma | NI | NI | NI | 2 |
| 63 | África do Sul | F | 72 | Melanoderma | NI | NI | NI | 3 |
| 64 | África do Sul | F | 57 | Melanoderma | NI | NI | NI | 3 |
| 65 | África do Sul | F | 53 | Melanoderma | NI | NI | NI | 3 |
| 66 | África do Sul | F | 50 | Leucoderma | NI | NI | NI | 3 |
| 67 | África do Sul | F | 49 | Leucoderma | NI | NI | NI | 2 |
| 68 | África do Sul | F | 62 | Melanoderma | NI | NI | NI | 3 |
| 69 | África do Sul | F | 55 | Melanoderma | NI | NI | NI | 3 |
| 70 | África do Sul | F | 66 | Melanoderma | NI | NI | NI | 3 |
| 71 | África do Sul | F | 51 | Melanoderma | NI | NI | NI | 3 |
| 72 | África do Sul | F | 36 | Leucoderma | NI | NI | NI | 2 |
| 73 | África do Sul | F | NI | Melanoderma | NI | NI | NI | 2 |
| 74 | África do Sul | F | 35 | Melanoderma | NI | NI | NI | 2 |
| 75 | África do Sul | F | 34 | Melanoderma | NI | NI | NI | 2 |
| 76 | África do Sul | F | 51 | Melanoderma | NI | NI | NI | 3 |
| 77 | África do Sul | F | 46 | Melanoderma | NI | NI | NI | 3 |
| 78 | África do Sul | F | 52 | Leucoderma | NI | NI | NI | 3 |
| 79 | África do Sul | F | 64 | Melanoderma | NI | NI | NI | 3 |
| 80 | Guatemala | F | 46 | NI | NI | NI | NI | 2 |
| 81 | Guatemala | F | 45 | NI | NI | NI | NI | 2 |
| 82 | Guatemala | F | 44 | NI | Sim | NI | Sim | 2 |

F = Feminino; M = Masculino; NI = Não informado; EUA = Estados Unidos da América

## APÊNDICE 2

### TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

**Convite:** Convido o(a) Senhor(a) a participar de forma livre, espontânea e esclarecida na pesquisa " AVALIAÇÃO CLINICO-PATOLÓGICA E RADIOGRÁFICA DE PACIENTES AFETADOS POR DISPLASIA ÓSSEA FLORIDA – ESTUDO RETROSPECTIVO E MULTICÊNTRICO". O responsável pela pesquisa, pelas informações contidas neste Termo de Consentimento Livre e Esclarecido (TCLE), bem como quem fará a apresentação e obtenção da autorização dos pacientes, objeto desse estudo, é a Cirurgião-Dentista, Débora Lima Pereira, aluna do curso de Mestrado em Estomatopatologia da Faculdade de Odontologia de Piracicaba-UNICAMP.

**Justificativa:** A displasia óssea florida (DOFlo) é uma doença bem conhecida em diversas partes do mundo, porém, não existem estudos multicêntricos internacionais correlacionando suas principais características. O presente trabalho pretende analisar pacientes afetados com esse tipo de lesão em 4 diferentes países através de dados clínicos, radiográficos e histopatológicos correlacionando com a etnia e os costumes do país de origem. Esse estudo visa também trazer informações novas e relevantes quanto a DOFlo e caracterizar melhor essa doença no mundo.

**Objetivos da pesquisa:** O objetivo do estudo é avaliar os aspectos étnicos, clínicos, radiográficos e histopatológicos de pacientes com DOFlo diagnosticados em 5 diferentes centros de diagnósticos de 4 países, incluindo África do Sul, Brasil, EUA e Guatemala, e correlacionar as principais características radiográficas em diferentes etnias.

**Metodologia**: O presente estudo será desenvolvido na Faculdade de Odontologia de Piracicaba na Universidade Estadual de Campinas (FOP-UNICAMP) baseado em uma análise retrospectiva (dados e exames já coletados) envolvendo 200 pacientes de 4 países diferentes (África do Sul, Brasil, Estado Unidos e Guatemala). A análise será principalmente baseada em radiografias panorâmicas de arquivos dos centros de diagnóstico. Além disso, radiografias periapicais, tomografias computadorizadas e lâminas histopatológicas provenientes de biópsias de DOFlo que forem disponíveis também serão analisadas por pelo menos 2 pesquisadores.

**Desconforto e riscos:** Não há riscos previsíveis por participar dessa pesquisa.

**Benefícios:** Não há benefícios diretos para os sujeitos participantes desta pesquisa. Os dados obtidos na pesquisa poderão ser importantes para colaborar com o melhor entendimento da doença e suas características, bem como as condutas a serem tomadas, ao redor do mundo em novos pacientes diagnosticados com a lesão.

**Telefone, endereço e e-mail do pesquisador responsável:** (19) 2106-5266 e (11) 95358 3507; Av. Limeira 901, FOP-UNICAMP, CEP 13414-903, Piracicaba – SP, debora.lpereira@gmail.com

"Em caso de dúvidas quanto aos seus direitos como voluntário de pesquisa entre em contato com o Comitê de Ética em Pesquisa da FOP: Av. Limeira 901, FOP-UNICAMP, CEP 13414-903, Piracicaba – SP, Fone/Fax 19-21065349, e-mail: CEP@fop.unicamp.br e webpage www.fop.unicamp.br/cep".

**Garantias:** Você terá o esclarecimento necessário de qualquer parte do estudo antes, durante e após a realização da pesquisa. Baseado nas informações fornecidas tem o direito de se recEUAr a participar na pesquisa, ou retirar o consentimento, a qualquer momento, sem que isto acarrete qualquer penalidade ou represália de qualquer natureza e sem que haja prejuízo ao tratamento iniciado ou por iniciar. Não há grupo controle ou placebo nesta pesquisa e não há forma alternativa de obtenção das informações desejadas.

Sua identidade, bem como todos os dados ou informações fornecidas serão consideradas confidenciais e mantidas em sigilo. A participação na pesquisa não gera despesa ao voluntário, portanto não há previsão de ressarcimento. Uma cópia do presente Termo de Consentimento Livre e Esclarecido será entregue ao participante voluntário.

**Consentimento**

Eu, _____, Identidade Nº _____, Telefone: _____, certifico que, após a leitura deste documento e de outras explicações dadas pelo pesquisador responsável, sobre os itens acima, estou de acordo em participar da realização dessa pesquisa.

Piracicaba, _____ de _____ de 201_.

Assinatura do Paciente_____

Assinatura do pesquisador:_____

## APÊNDICE 3

Artigo publicado no periódico General Dentistry [2016 Mar-Apr;64(2):21-5]

Peer-Reviewed Journal of the Academy of General Dentistry
GENERAL DENTISTRY

**Florid Osseous Dysplasia associated with multiple simple bone cysts: A patient with 22 years of follow-up**

| | |
|---|---|
| Journal: | *General Dentistry* |
| Manuscript ID | GD-2015-0104.R1 |
| Manuscript Type: | Case Study |
| Specialties and Areas of Interest: | 319 Biopsies < 310 Oral and Maxillofacial Surgery, 734 Diagnosis & Treatment Planning - General < 730 Oral Medicine, Oral Diagnosis, Oral Pathology, 739 Diagnosis of Oral Pathology < 730 Oral Medicine, Oral Diagnosis, Oral Pathology, 741 Management of Hard & Soft Tissue Lesions < 730 Oral Medicine, Oral Diagnosis, Oral Pathology |
| | |



# Florid Osseous Dysplasia associated with multiple simple bone cysts: A patient with 22 years of follow-up

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**Abstract**

Florid osseous dysplasia (FOD) has been described as a condition that typically affects the jaws of middle-aged afrodescedent women, and usually presents as multiple radiopaque masses distributed throughout the jaws. The diagnosis is generally based on clinic and radiological presentation often involving various regions of the jaws without evident bone expansion. The current paper describes a FOD case in a 27-year-old African-American woman with 22 years of follow-up displaying the dynamic radiographic character of this entity and the unusual co-occurrence with multiple simple bone cysts. These data reinforce the importance of long-standing follow-ups in patients diagnosed with FOD.

**Keywords:** Florid Osseous Dysplasia, Simple Bone Cyst.

## Introduction

Florid osseous dysplasia (FOD) is a relative uncommon benign fibro-osseous condition of the jaw bones that was first described by Melrose, Abrams and Mills in 1976 [1].These lesions are most commonly seen in middle-aged afrodescendent women, although it also may occur in Caucasians and Asians. The etiology is unknown [2–5], but it has been suggested to represent reactive or dysplastic processes originating from elements of the periodontal ligaments [6–8]. Although FOD is usually asymptomatic, occasionally some patients present pain, which is normally associated with local infection. Discreet bone expansion and more rarely facial deformities may also be observed [8-10].

Radiographically, FOD often develops as circumferential radiolucency surrounding the root apices of vital teeth and over the time assumes a mixed aspect (radiolucent-radiopaque) and becomes increasingly radiopaque. The lesions are located in two or more quadrants and have a striking tendency to be bilateral. It is not unusual to find extensive lesions in all four quadrants of the maxillas and mandible [2,11-13]. As a complementary examination, computed tomography (CT) can be useful for FOD evaluation because of its ability to acquire axial, sagittal, and frontal views [12,14,15]. In many cases, the lesion is detected when dental radiographs are taken for some purposes other than the investigation of jaw lesions.

The diagnosis is normally based on the clinic and radiographic presentation. However, biopsy or surgical intervention may rarely be necessary allowing microscopic analysis, which is characterized by anastomosing bone trabeculae and layers of cementum-like calcifications embedded in a fibroblastic background [16].
The management of asymptomatic FOD cases consist basically in periodic clinic and radiographic evaluation [8,11]. In patients who present secondary infection of FOD with purulent drainage, systemic antibiotic is necessary. Yet, because of the avascular nature of the FOD, infection may persist and sequestrectomy be recommended [10,11].

To the best of our knowledge, the current report presents the longest follow-up of a patient with FOD in association with multiple simple bone cysts published in the English-language literature, describing its singular radiographic features.

**Case Report**

A 27-year-old African-American female patient was referred to our Oral Medicine Clinic with a complaint of a swelling in the mandible that has been present for 2 years. The patient has also referred a slight pain in the region for about 1 month. She had unremarkable medical history and her physical examination showed no significant abnormality. Intraoral examination revealed partially edentulous areas and no cortical bone expansion. Overlying gingiva and oral mucosa were normal without any clinical signs of alteration.

On the first panoramic radiographic examination performed in 1992, three different radiolucent areas were observed in the mandible. One image in the right side of the mandibular body involving an edentulous area as well as the roots of the second molar, another image in the left mandibular body (edentulous area) and a third image involving the apex of the right canine and lateral and central incisors. In addition, it seems that there are diffuses and slight radiopaque areas in the left maxilla and in the posterior mandible, left side (Fig. 1).

At this moment, the clinical and radiographical hypothesis of diagnosis was multiple odontogenic keratocysts, particularly because the absence of bone expansion and the multiple presentation of the lesion. Therefore, surgical exploration was performed in two of these lesions (body of the mandible in both sides) and empty bone cavities were found, which were suggestive of simple bone cyst (SBC). Small fragments of tissue were curetted and histopathological analysis showed vital bone and blood clots consistent with the diagnosis of SBC. The third lesion involving the right canine and incisors was just followed. After 2 years of follow-up, there was bone formation in the surgically addressed areas (Fig. 2). However, due to complaints of pain and mild swelling on the right side of the mandible, new surgical exploration was carried out and SBC was diagnosed again. Regarding the image around the apex of the right canine and incisors it was observed enlargement of the radiolucent area. Pulp vitality test was performed and displayed negative results for the canine and lateral incisor. The patient was referred for endodontic treatment. Although the anterior radiolucent area continued unchanged in the following 2 years, and it was decided for the clinical and radiographic follow-up.

Monitoring the patient in the following 5 years (1994-1999) a significant change in the bone pattern of the mandible was observed, with mixed radiolucent

areas in the anterior region and in the right side of mandibular body. On the left side, it was observed increased of dispersed sclerotic images in the mandible and a radiopaque area at the upper quadrant (Fig. 3). At this moment, the diagnosis of Florid Osseous Dysplasia became more evident.

Due to the patient complain of the persistent swelling in the bone and mild pain, other two other exploratory biopsies were performed at the radiolucent regions (one in the lower posterior right region and another in the anterior region of the mandible). In both sites it was observed empty bone cavity with blood clots compatible with SBC. Histological examination confirmed this diagnosis.

In the following 8 years (1999-2007) it was noticed an intense change in the radiographic bone pattern of the mandible with development of other radiolucent areas suggestive of SBC. It was decided for two additional biopsies, one in the right mandibular body and another in the left lower incisors and premolars regions, where there was an extensive radiolucent area involving the roots of the teeth in these sites (Figs. 4-6). Again, it was found empty bone cavities. A year later, the panoramic radiography showed almost complete bone formation throughout the mandible, with some diffuse sclerotic areas (Fig. 7). After 3 years, there were no significant changes (2008-2011). From the year 2012 until 2014, the lesions remained stable with a mixed radiopaque pattern in the mandibular body and an irregular radiolucent area involving all the roots of the lower anterior teeth (Fig. 8). However, during these 22 years of follow-up, even with several surgical procedures no signs of infection were found. The patient has been monitored on regular basis and conventional dental treatment has been performed when necessary. Table I presents a summary of the seven associated simple bone cysts.

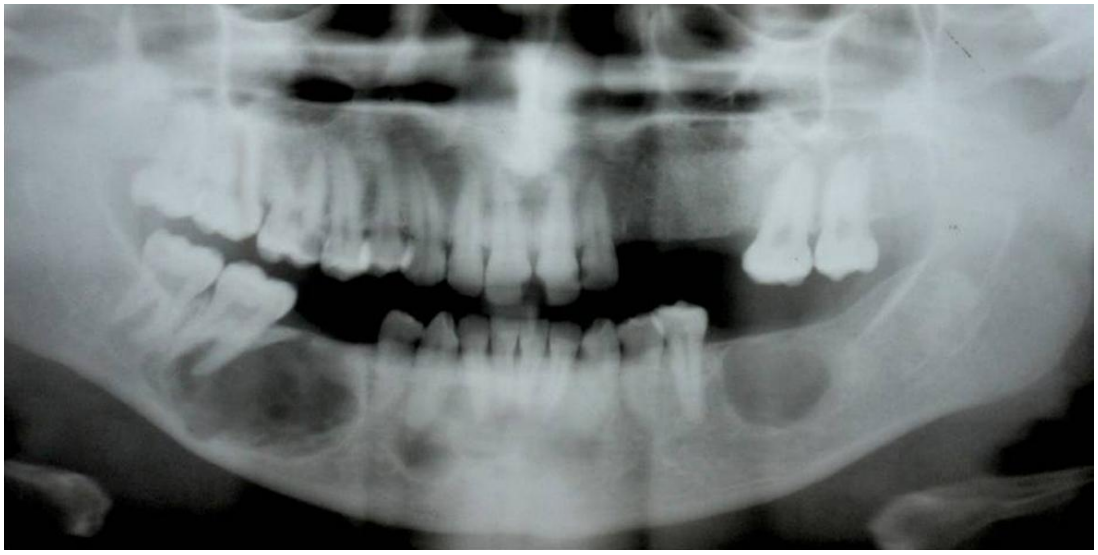

**Figure 1 -** First panoramic radiograph (1992). Three distinct radiolucent areas were observed in the mandible. Surgical exploration was performed in two of these lesions (body of the mandible in both sides) and diagnosis was simple bone cyst. The third lesion involving the apex of the right canine and lateral and central incisors was just followed.

**Figure 2 -** Panoramic radiograph (1994). Almost complete bone formation in both sides of mandibular body, areas that were surgically addressed.

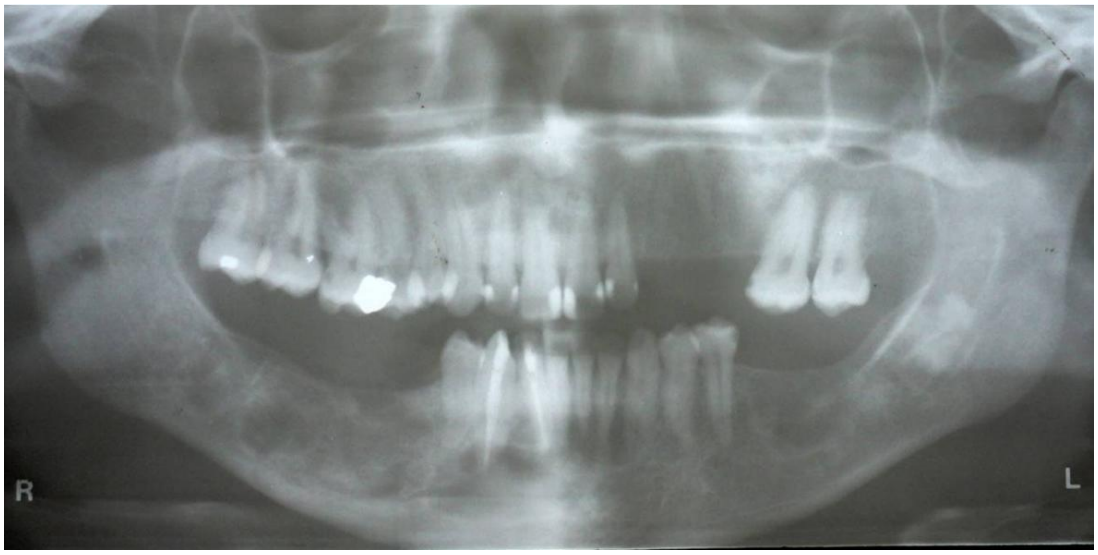


**Figure 3 -** Panoramic radiograph three years later (1997) showed significant change in the trabecular pattern, with mixed radiolucent areas in the anterior region and in the right side of mandibular body. On the left side, increased of dispersed sclerotic images in the mandible and a radiopaque area at the upper quadrant were noticed.

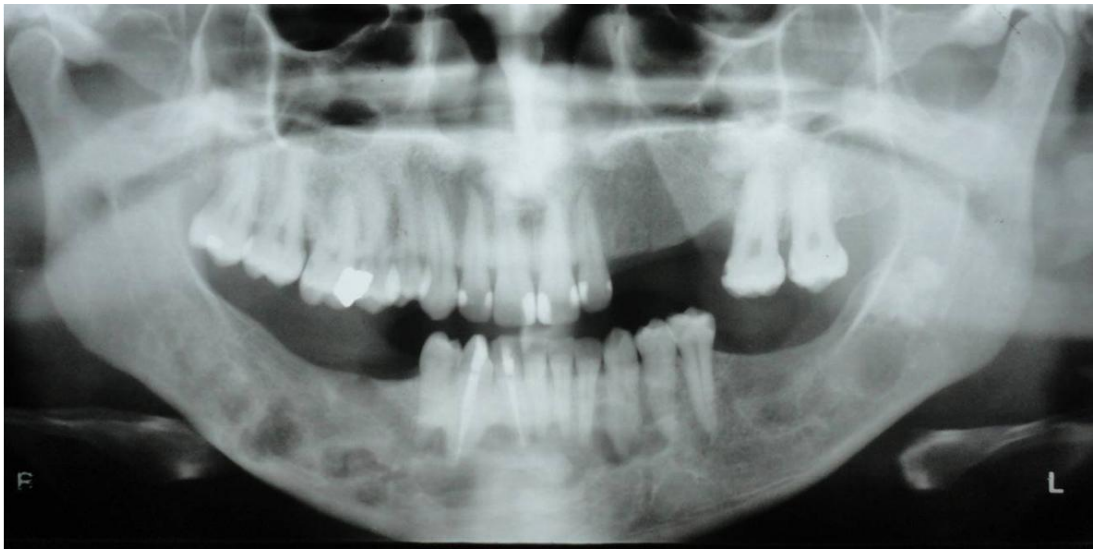


**Figure 4 -** Panoramic radiograph (2002). Different pattern compared to previous radiographs showing more radiolucent areas in the mandibular body left and right sides.

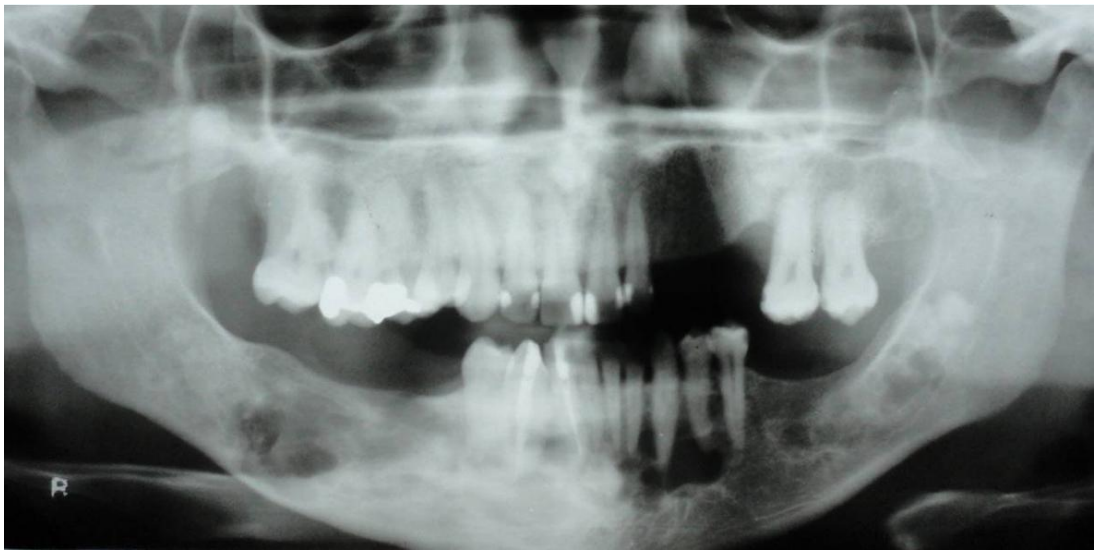


**Figure 5 -** Panoramic radiograph (2004). Change in the radiographic pattern displaying increasing of the radiolucent areas in the mandibular body.


**Figure 6 -** Panoramic radiograph (2006). An extensive radiolucent area involving the roots of the lower left incisors and premolars as well as the right mandibular body were observed. Two additional biopsies were performed and the diagnosis was again simple bone cyst.

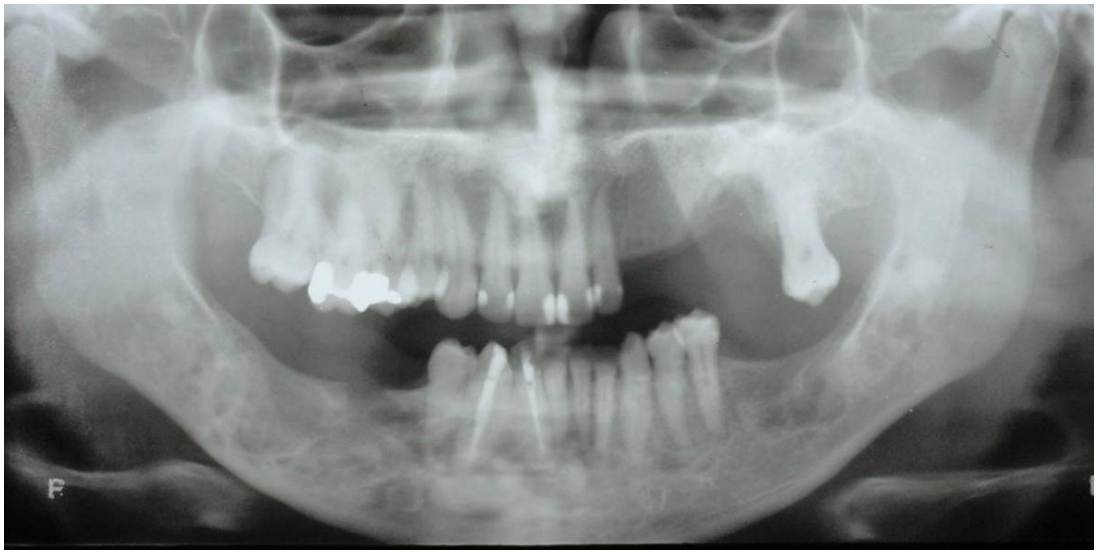

**Figure 7 -** Panoramic radiograph (2008). Almost complete bone formation throughout the mandible.

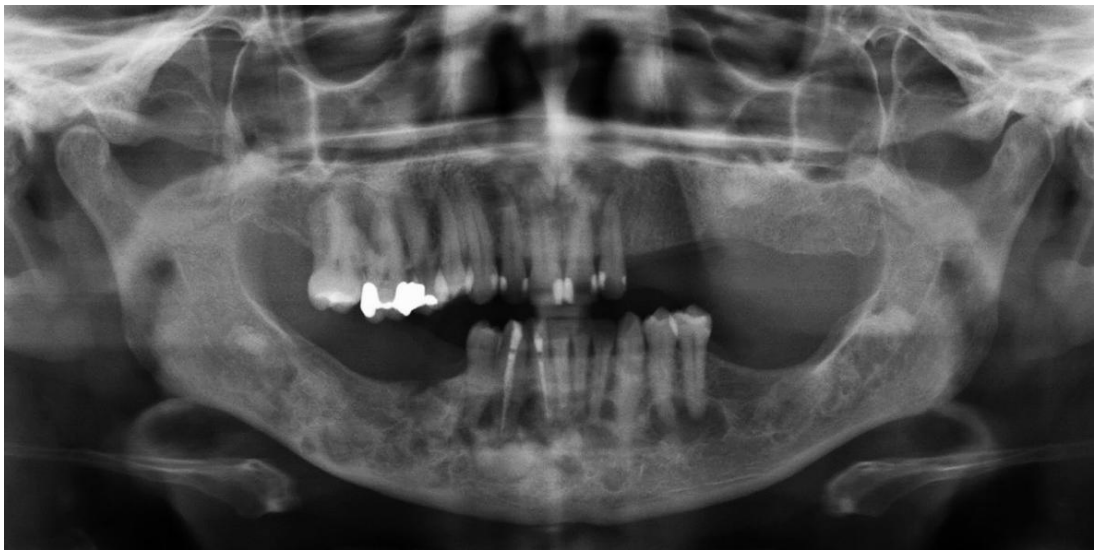

**Figure 8 -** Panoramic radiograph (2014). Different radiographic pattern compared to previous figure, showing a mixed radiographic pattern in the mandibular body and an irregular radiolucent area involving all the roots of the lower anterior teeth.

**Table I –** Summary of the location and radiographic aspects of seven simple bone cysts diagnosed in the current patient.

| **Date** (Month/Year) | **Location** | **Radiographic aspects** | **Histopathological diagnosis** |
|---|---|---|---|
| 09/1992 | Mandible right side | Well defined multilocular - mixed radiopaque/radiolucent | Simple bone cyst |
| 10/1992 | Mandible left side | Well defined unilocular radiolucent | Simple bone cyst |
| 07/1994 | Mandible right side | Diffuse - mixed radiopaque/radiolucent | Simple bone cyst |
| 05/1999 | Mandible right side | Diffuse – mixed radiopaque/radiolucent | Simple bone cyst |
| 07/1999 | Mandible anterior | Diffuse – mixed radiopaque/radiolucent | Simple bone cyst |
| 06/2007 | Mandible right side | Diffuse – mixed radiopaque/radiolucent | Simple bone cyst |
| 09/2007 | Mandible anterior | Well defined multilocular radiolucent | Simple bone cyst |

## Discussion

In the current classification of bone-related lesions, released in 2005 by the World Health Organization, osseous dysplasias (OD) are described as idiopathic processes located in the periapical region of tooth-bearing jaw areas, characterized by the replacement of normal bone by fibrous tissue and metaplastic bone. This condition occurs in various clinical forms. When OD occurs in the anterior mandible and involves only a few adjacent teeth, it is called periapical osseous dysplasia. A similar limited lesion occurring in a posterior jaw quadrant is named focal osseous dysplasia. Two other types of OD are more extensive: FOD and familial gigantiform cementoma, which occurs bilaterally in the mandible or sometimes involving all 4 jaw quadrants [17].

The radiographic pattern of FOD can be extremely variable, and the long follow-up may show a wide spectrum ranging from radiolucent to almost complete

radiopacity. Therefore, FOD has been described as having three developmental stages, each one with its specific radiographic features. In the early or osteolytic stage, radiographs show a well-defined radiolucent area with loss of periodontal ligament and lamina dura. In the intermediate or cementoblastic stage, small opacities appear within the radiolucent area, which consequently displays a mixture of radiolucent and radiopaque architecture. The last and more mature stage is called osteosclerotic or “inactive” stage, is characterized by only radiopacity, presented in the major part of the lesion [18].

FOD can resemble other forms of osseous dysplasias, other benign fibro-osseous lesions such as ossifying fibroma, fibrous dysplasia, chronic diffuse sclerosing osteomyelitis, Paget´s disease as well as inflammatory endodontic lesions. In most situations, the diagnosis may be particularly confusing during the early stages, when it can be misdiagnosed as an asymptomatic periapical disease because of the localized periapical radiolucency [19-23]. Vitality tests of related teeth are essential in order to avoid unnecessary endodontic therapy. However, these tests can be subjective and confusing, leading to false negative results. In the current case, two teeth with no evident cause for pulp necrosis such as deep caries or restorations were endodontically treated, which probably occurred because of the false negative vitality test. The presence of a radiolucent area mimicking a periapical lesion might have misled the dentist to a wrong diagnosis. Therefore, it is extremely important that patients with radiographic alterations be evaluated by an expert professional in order to establish the appropriate differential diagnosis and to assure and/or predict the least invasive procedures.

Biopsy should be avoided in asymptomatic lesions to prevent the risk of bone infection, osseous sequestration and non-healing wounds. However, surgical exploration may be necessary to remove bone sequestrum or to investigate non-characteristic bone alteration. In this context, Melrose et al. [1], were the first to observe the association between simple bone cyst (SBC) and FOD. In their series of 34 cases of FOD, 17 biopsy-proven simple bone cysts were found in 14 studied patients [1,24]. Melrose et al. [1] also reported that pain or a dull aching sensation was experienced at the site of SBC in five out of fourteen patients. In the current case, the patient also complained constantly of a swelling in the mandible and a slight pain.

Radiographically, a classic SBC is recognized as well-defined intraosseous radiolucencies that often extend between the teeth roots of young patients. It presents clinically as empty cavities and the mandibular body is usually affected (75%), mainly in the pre-molar and molar regions [25]. However, as shown by Sabino-Bezerra et al. [26], although rare, atypical presentations of SBC may occur. In their series, several lesions were extensive and presented cortical bone resorption and none of the cases was radiographically considered to be SBC. Horner & Forman [27] reported 4 cases of atypical simple bone cysts of the jaw and in 3 of them there was association with periapical cement-osseous dysplasia. In these situations, the patients are often older than the patients who have typical SBC.

Melrose et al. [1] reported that SBC in patients with FOD often manifest active enlargement and do not always respond to the usual therapeutic methods. In addition, when it heals, the radiographic appearance of the mineralized tissue is often abnormal. In the current case, 7 exploratory surgeries were performed in an interval of 15 years and had the diagnosis of SBC (Table I) and in bone neo-formation was observed in all of them.

Other lesions including malignant tumors arising in association with FOD have also been reported. Schneider et al. [28] showed a spindle cell malignancy diagnosed in the mandible affected by FOD. In other study, Lopes et al. [5] reported a high-grade osteosarcoma arising in the mandible in a patient diagnosed as FOD.

## Conclusion

In summary, systematic long-term follow-up by a specialist professional is extremely important for all patients diagnosed with OD, including FOD, in order to observe radiographic changes. The detection of any possible associated lesion, as well as a correct intervention when necessary, is crucial for appropriate management of these patients.

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14-Oct-2015

Dear Prof. Lopes,

Thank you for the submission of your manuscript, "Florid Osseous Dysplasia associated with multiple simple bone cysts: A patient with 22 years of follow-up," to General Dentistry. It has been evaluated by the reviewers and we are pleased to inform you that **it has been accepted for publication in General Dentistry.**

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Editor

Dear Dr. Lopes,

Thank you for your submission to *General Dentistry.* Your article, ***Florid Osseous Dysplasia associated with multiple simple bone cysts: A patient with 22 years of follow-up***, has been assigned to the January/February 2016 issue of *General Dentistry*. The Editor reserves the right to change dates of publication, as well as not publish accepted manuscripts. Should your date of publication need to be altered, we will contact you as soon as possible. **Please confirm receipt of this email and your continued interest in publishing your manuscript in *General Dentistry.***

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## ANEXO 1

Certificado do Comitê de Ética em Pesquisa da Faculdade de Odontologia de Piracicaba – UNICAMP

**COMITÊ DE ÉTICA EM PESQUISA**
**FACULDADE DE ODONTOLOGIA DE PIRACICABA**
**UNIVERSIDADE ESTADUAL DE CAMPINAS**

CERTIFICADO

O Comitê de Ética em Pesquisa da FOP-UNICAMP certifica que o projeto de pesquisa **" Avaliação clínico-patológica e radiográfica de pacientes afetados por displasia óssea florida - estudo retrospectivo e multicêntrico"**, protocolo nº 043/2014, dos pesquisadores Débora Lima Pereira, Fabio Ramôa Pires, Marcio Ajudarte Lopes e Pablo Agustin Vargas, satisfaz as exigências do Conselho Nacional de Saúde - Ministério da Saúde para as pesquisas em seres humanos e foi aprovado por este comitê em 11/06/2014.

The Ethics Committee in Research of the Piracicaba Dental School - University of Campinas, certify that the project **"Clinicopathological and radiological evaluation of patients affected by florid osseous dysplasia – a multicenter retrospective study"**, register number 043/2014, of Débora Lima Pereira, Fabio Ramôa Pires, Marcio Ajudarte Lopes and Pablo Agustin Vargas, comply with the recommendations of the National Health Council - Ministry of Health of Brazil for research in human subjects and therefore was approved by this committee on Jun 11, 2014.

**Prof. Dr. Felippe Bevilacqua Prado**
Secretário
CEP/FOP/UNICAMP

**Profa. Dra. Lívia Maria Andaló Tenuta**
Coordenadora
CEP/FOP/UNICAMP

Nota: O título do protocolo aparece como fornecido pelos pesquisadores, sem qualquer edição.
Notice: The title of the project appears as provided by the authors, without editing.

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