# Quantification of bone gain in central giant cell granuloma of the jaws submitted to intralesional corticotherapy

Quantificação de ganho ósseo em lesões centrais de células gigantes dos maxilares submetidas à corticoterapia intralesional

Israel L. Cavalcante<sup>1</sup>; Caio César S. Barros<sup>2</sup>; Karol A. M. Rodrigues<sup>1</sup>; Rafael L. V. Osterne<sup>3</sup>; Roberta B. Cavalcante<sup>1</sup>; Renato M. Nogueira<sup>3</sup>; Renata C. T. Medeiros<sup>1</sup>

1. Universidade de Fortaleza (Unifor), Ceará, Brazil. 2. Universidade Federal do Rio Grande do Norte (UFRN), Rio Grande do Norte, Brazil.
3. Universidade Federal do Ceará (UFC), Ceará, Brazil.

#### **ABSTRACT**

Introduction: The central giant cell granuloma (CGCG) is a bone alteration of unknown etiology that can affect the jaws and presents varied clinical behavior. Objective: To analyze radiographs from patients with CGCG submitted to intralesional corticosteroids, in order to quantify bone gain after treatment. Methods: Sixteen patients with the microscopic diagnosis of CGCG were selected from the Batista Memorial Hospital, in Fortaleza, Ceará, Brazil. Thirty-two radiographs (16 initial and 16 final) were evaluated by the mean pixel values of the affected region before and after the complete corticosteroid intralesional application protocol (six applications in biweekly intervals of triamcinolone hexacetonide). Results: Of the patients submitted to the study, 14 (87.5%) presented a mean increase in the values of pixels, understood as bone gain, in the radiographs after treatment with intralesional injections, and two (12.5%) did not present it. The comparison of the mean pixel values between the initial and final test sides showed p = 0.0027, which was statistically significant, confirming the increase in density in the studied regions. Conclusion: The tools for analysis of pixel values were useful in the quantification of bone gain in patients submitted to intralesional corticosteroid therapy, and these tools should be further explored and used during treatment as auxiliary methods in the evaluation of its efficacy.

Key words: therapeutics; radiography panoramic; diagnosis.

#### **INTRODUCTION**

The central giant cell granuloma (CGCG) is a non-odontogenic condition that represents around 10% of all benign jaw lesions. It has an incidence of 0.0001% in the general population, and was first described by Jaffe in 1953<sup>(1)</sup>. CGCGs tend to occur in young patients, under the age of 30, having been reported in children up to 2 years, with a slight predilection for females<sup>(2-6)</sup>.

Clinical and radiographic findings show a wide spectrum of behavior, ranging from aggressive to non-aggressive<sup>(2)</sup>. Non-aggressive lesions are characterized by no symptoms, slow growth, absence of cortical perforation, and low recurrence rate. Aggressive lesions, less common, are associated with pain, rapid growth,

cortical perforation, root resorption and high recurrence rates<sup>(7)</sup>. CGCGs can appear as unilocular or multilocular radiolucencies, of well-defined or ill-defined margins and varied degrees of cortical expansion. They can be confused with other jaw lesions, such as brown tumor of hyperparathyroidism, fibrous dysplasia, aneurysmal bone cyst, and other fibro-osseous lesions<sup>(3,8)</sup>.

The most common treatment for CGCGs is still curettage<sup>(9-13)</sup>, which can be used along with cryosurgery, in some cases<sup>(14)</sup>, and with peripheral ostectomy, in others<sup>(2)</sup>. Although the surgical treatment is still widely recommended, daily systemic doses of calcitonin<sup>(10, 11)</sup> and intralesional injections of corticosteroids<sup>(15)</sup> have been increasingly investigated. The corticosteroid intralesional injection causes the decrease of the lesion and even the resolution of the case, being a conservative, simple and low-cost treatment.

While conservative treatment shows favorable results, bone gain is assessed just visually by means of radiographic images, and no form of quantification of such a gain is established (15-20). Therefore, the objective of this study was to analyze radiographs from patients with CGCG who underwent intralesional corticotherapy, aiming at quantifying post-treatment bone gain.

#### **METHODS**

This study was conducted with prior approval by the Ethics Research Committee (protocol no.79/08). The studied population was composed of patients with histopathological diagnosis of CGCG registered in the files of Hospital Batista Memorial de Fortaleza, Ceará, Brazil. Patients included in the sample were those with: complete identification, clinical information on the existence or not of symptoms, description of clinical signs, and imaging tests with initial and follow-up panoramic radiographs. Patients were excluded when diagnosed with brown tumor of hyperparathyroidism or cherubism, as well as when errors in radiographic technique, patient positioning or radiograph processing occurred.

## Analysis of clinical data

For analysis of clinical data, information were gathered about type of adopted treatment, lesion site, microscopic characteristics obtained from incisional biopsy (**Figure 1**) and data relative to patient follow-up. The overall analysis of available data in each case was intended for a better evaluation of response to treatment, besides correlation with radiographic data.

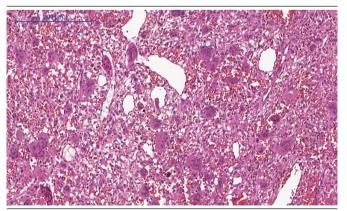


FIGURE 1 – Microscopic aspects of CGCG: proliferation of mononuclear mesenchymal cells associated with a population of multinucleated giant cells in a matrix of dense fibrous conjunctive tissue, presenting extravasated red blood cells (HE, 200 µm)

CGCG: central giant cell granuloma; HE: bematoxylin and eosin.

## Radiographic assessment

Radiographs were scanned at an optical scanner PowerLook II (Techville - Dallas-USA) with spatial resolution of 600 dpi, and analyzed with the program ImageJ<sup>®</sup> [1.29× (NIH-USA)] at a flat-screen computer (Sony LED screen 15.5"- Intel Core i3-2350M).

Images were opened at a computer that runs on Windows® platform, and the room was darkened during radiograph analysis, for better visualization. Similarly to what was performed by Teixeira *et al.* (2011)<sup>(21)</sup>, in each of the images, an area corresponding to the region of interest (ROI) was opened in the oval format and saved so that its size and format could be maintained in all measurements for each of the studied patients.

Two distinct regions of the same image were selected. One presented healthy bone, being considered bone image of initial control; the other, containing affected bone, was designated initial test area. Later, both regions were compared to the same areas evaluated after the complete protocol of intralesional corticoid (six biweekly applications of triamcinolone hexacetonide) application, aiming at assessing bone gain after the employed treatment (**Figures 2** and **3**). Using the resources of ImageI® program, the mean pixel values of the evaluated area and its standard deviation (SD) were recorded, according to data provided by the histogram. Such a measure was taken both in the test area (undergoing corticotherapy) and in the control area, in the 32 images (16 initial and 16 final). The examiner was allowed to adjust brightness and contrast of the visualized image. The histogram of ImageJ® software provided data on the mean pixel values at a scale of 8 bits, attributing the zero value to the darkest grey (black) and 255 to the lightest (white). The ROI measures were obtained by two examiners separately, obeying the same technique.

A second analysis was conducted, 30 days later, for the evaluation of intraexaminer and interexaminer agreement, and the obtainment of reproducibility of pixel value measurements by means of the histogram. In case of different values, an average of the procedure was taken. After obtainment of a mean pixel value of the test and control areas, subtraction between the value on the control side and the test side was conducted (ROI test - ROI control), aiming at the control area to have a value always equivalent to zero, to minimize variations inherent in radiographic exposure and processing, both in initial and final images. Next, a comparison of the initial result was done with the final result (ROI final test - ROI initial test) aiming at quantifying bone gain in that region. The mean pixel values of initial and final test sides were submitted to the Friedman test in Bioestatic 5.0 program, in which a significance level of 5% ( $\alpha = 0.05$ ) was adopted.

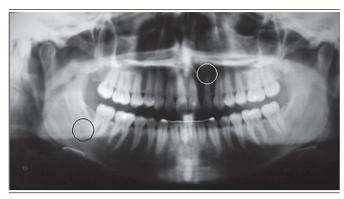


FIGURE 2 – Panoramic radiograph prior to treatment: ROI test (white circle) and initial control (black circle) in the area before intralesional corticosteroid application ROI: region of interest.



FIGURE 3 – Post-treatment panoramic radiograph: ROI test (white circle) and final control (black circle) after the protocol of intralesional corticosteroid application ROI: region of interest.

## **RESULTS**

In the present study, from a universe of 32 patients, 16 met the inclusion criteria of the study and had their panoramic radiographs undergoing analysis for bone gain quantification. Females were more affected (n=10;62.5%) than males at a F:M ratio of 1.6:1. The age of patients included in the study ranged from 7 to 25 years, with an average of 16.3 years.

Regarding complaints, all patients presented volumetric increase of the involved area, just four (25%) reported pain, and just one patient (6.25%) reported paresthesia. Ten cases involved the mandible (62.5%); and six, the maxilla (37.5%).

The radiographs revealed 12 patients (75%) presenting unilocular lesions; and the remaining (25%), multilocular lesions. Among the 16 patients, 12 (77.7%) presented tooth displacement; four (25%), tooth resorption; seven (43.75%), cortical perforation; and 14 (67.5%), cortical expansion (**Table 1**).

The defined ROI was used in the measurement of mean pixel values of test and control side images of each patient. Of the 16 cases, 14 (87.5%) presented increased mean pixel values — understood as bone gain in radiographs after treatment with intralesional injections —, and just two (12.5%) did not present this picture. Comparison of mean pixel values between initial and final test sides, described in **Table 2**, showed statistically significant difference (p = 0.0027).

Sex Site Pain Cortical expansion Tooth displacement Tooth resorption Patient Age Cortical perforation Patient 1 Male 10 Mandible No Yes Yes No No Patient 2 Maxilla Female 24 Yes No Yes No No Patient 3 Female 21 Mandible Yes Yes Yes Yes Yes Patient 4 Male 20 Maxilla No Yes No No No Patient 5 Female 19 Mandible No Yes No No No Patient 6 Male 9 Maxilla No Yes Yes No Yes Patient 7 Female 15 Mandible Yes Yes Yes Yes Yes Patient 8 Male 12 Mandible No Yes Yes No No Patient 9 Female 24 Mandible No Yes No No No Patient 10 Female 20 Maxilla Yes Yes Yes No Yes Patient 11 Female 9 Maxilla No Yes Yes No No Patient 12 Male 7 Maxilla No Yes Yes No No Patient 13 Male 25 Mandible No No No No Yes Patient 14 Female 9 Mandible No Yes Yes No No

TABLE 1 - Criteria adopted in CGCG classification, according to biological behavior

Criteria used by Chuong et al. (1986)(22).

Female

Female

18

19

Mandible

Mandible

Patient 15

Patient 16

Yes

Yes

Yes

Yes

Yes

Yes

Yes

Yes

No

Yes

TABLE 2 – Mean initial and final pixel values, by patient

		1 / / 1	
Data	Mean initial pixel values	Mean final pixel values	Result
Patient 1	-55.347	-14.278	41.069
Patient 2	- 113.976	73.408	187.384
Patient 3	- 112.468	87.596	200.064
Patient 4	-126.287	-115.515	10.772
Patient 5	-95.212	9.594	104.806
Patient 6	57.52	118.965	61.445
Patient 7	- 128.351	30.04	158.391
Patient 8	-6.209	28.188	34.397
Patient 9	-52.619	-28.417	24.202
Patient 10	-21.012	-59.995	-38.983
Patient 11	- 39.004	30.845	69.849
Patient 12	60.175	77.035	16.86
Patient 13	- 44.941	7.214	52.155
Patient 14	-78.135	33.694	44.441
Patient 15	11.659	3.096	-8.563
Patient 16	-56.089	-40.118	15.971

## **DISCUSSION**

According to Austin *et al.* (1959)<sup>(5)</sup>, CGCG represents less than 7% of all benign tumors of the jaws, but data relative to their occurrence are scarce in the literature. This low incidence hinders a better understanding of the lesion, as there are no studies with representative samples and a study with a large number of cases would be necessary for evaluation of the specific characteristics of aggressive and nonaggressive types, separately.

Nowadays, in search of more conservative treatments for several diseases, intraosseous corticotherapy has been employed successfully by some authors. However, there are no works in the literature that deal with quantification of bone gain when this treatment is employed, what would enable to prove the treatment success quantitatively. Pixel analysis by different programs has been reported in the literature, with quantification of pixel values being studied in different conditions<sup>(23)</sup>.

In the current study, 62.5% of the cases were female patients, what is in agreement with some authors that state there is a discrete predilection for this sex<sup>(7,23)</sup>. Patients' mean age was 16.3 years, what is also in agreement with the literature, which affirms that although the lesion can occur at any age, it affects mainly individuals in the first three decades of life<sup>(7,23,24)</sup>. The varied biological behavior of CGCG though, suggests that age group predilection is questionable, as it can be years for asymptomatic lesions to be identified, while symptomatic ones are rapidly diagnosed.

According to the literature, CGCGs affects principally the mandible, at a  $2:1^{(7, 23, 25)}$  proportion, similar to what was found

in the present study. Some authors report that lesions affect three times more often the mandible than the maxilla (8, 17, 24). At the current research, 62.5% of the cases occurred in the mandible, what is generally in compliance with the literature. Lesions affecting the maxilla are more common in the anterior portions, are confined to the region of the teeth and frequently cross the midline(26). Five of our cases presented in the anterior region of maxilla, crossing the midline. The other cases that involved the maxilla were limited to the left or right side of the face. Anatomical osseous aspects of the maxilla, such as the thin cortical plates and the mouth close proximity to open spaces and orbits influence prognosis and CGCG treatment(27). This statement allows us to understand why relapses are more frequent in the maxilla than in the mandible. In our work, one of the cases that responded negatively to treatment involved the maxilla, invading the nasal fossa, what made it difficult for the patient to breathe.

All patients underwent incisional biopsy, intralesional corticosteroid injections and final osteoplasty as treatment. Just one patient (5.55%), who presented local relapse of the lesion after corticoid treatment, underwent surgical curettage. The two patients that responded negatively to treatment were later referred to surgical treatment. In one of them the lesion was in the maxilla and invaded the nasal fossa, what made breathing difficult.

ROI analysis showed that mean pixel values increased in the final test side compared with the initial test side, a statistically significant result (p=0.0027), demonstrating the actual bone gain in follow-up radiographs when compared with initial radiographs. Just two cases (12.5%) did not display increased mean pixel values, what is in accordance with the clinical result, as they did not present good response to treatment, and needed additional treatment.

This study was conducted *in vivo* and presents great variability of radiographs regarding exposure and processing, what interfered in the analysis and results. This happened because it is a retrospective study, and inclusion and exclusion criteria were employed to minimize those variables. The participants' initial and final radiographic images were obtained in the same extraoral radiography equipment and were submitted to automatic processing.

The digitization process also seems to be very important so as not to lose information in the highest densities, as the subtle increased radiolucencies in incipient bone gain (28). At a scanner with specification of, for example,  $1200 \times 2400$  dpi, the smallest number corresponds to the optical resolution, and the dpi choice is a critical factor in the use of the scanner. In order to yield resolutions greater than the optical, an interpolation is done by means of

the program, what means calculating values that occur between two known values, adding new information to the image<sup>(29)</sup>. Thus, the direct digital radiography systems are the best option for the follow-up of these patients, what was not possible to do in the present study, for two reasons. First, because it is a retrospective study. Second, because most of our participants are low-income patients, treated in the public service, where radiographs not only present poor quality but are almost always conventional, needing to go through the digitization process.

In an effort to define treatment modality, the ideal would be applying molecular, biological or genetic markers able to establish the degree of aggressiveness of the lesion for each case. However, these parameters are not well defined, being the criteria by Chuong *et al.* (1986)<sup>(22)</sup> those used up to the moment.

For Kaban *et al.* (2002)<sup>(9)</sup> and Pogrel (2003)<sup>(13)</sup>, these factors must be taken into account for treatment choice: aggressive behavior versus non-aggressive behavior, site, size of the lesion,

and radiographic appearance. Yet, when non-surgical treatments are chosen, the forms of evaluating treatment efficacy, as bone gain quantification, have not, so far, been suggested in the literature.

Although surgery is the treatment of choice according to the literature, this does not seem the ideal treatment option, because it can cause mutilation and high morbidity, especially in children and young patients<sup>(30)</sup>.

## **CONCLUSION**

Tools for analysis of pixel values proved useful for bone gain quantification in patients submitted to intralesional corticoid treatment. They must be properly exploited and used along with the treatment. Besides, they permit dental surgeons to follow patients with more safety, evaluating whether treatment is being effective or not in each case.

#### **RESUMO**

Introdução: A lesão central de células gigantes (LCCG) é uma alteração óssea de etiologia desconhecida e comportamento clínico variado, que pode acometer os maxilares. Objetivo: Analisar radiografias provenientes de pacientes portadores de LCCG submetidos à corticoterapia intralesional, visando propor a quantificação de ganho ósseo pós-tratamento. Métodos: Foram selecionados 16 pacientes com diagnóstico microscópico de LCCG cadastrados nos arquivos do Hospital Batista Memorial de Fortaleza, Ceará, Brasil. Trinta e duas radiografias (16 iniciais e 16 finais) foram avaliadas por meio da média dos valores de pixels da região afetada pela afecção antes e após o protocolo completo de aplicação intralesional de corticoide (seis aplicações em intervalos quinzenais de triancinolona hexacetonida). Resultados: Dos pacientes submetidos à pesquisa, 14 (87,5%) apresentaram aumento da média dos valores de pixels — dado entendido como ganho ósseo — nas radiografias após tratamento com injeções intralesionais; apenas dois (12,5%) não apresentaram esse quadro. A comparação das médias dos valores de pixels entre os lados teste inicial e final mostrou p = 0,0027, o que foi estatisticamente significante, comprovando o aumento de densidade nas regiões estudadas. Conclusão: As ferramentas de análise de valores de pixels mostraram-se úteis na quantificação de ganho ósseo em pacientes submetidos à corticoterapia intralesional, devendo tais ferramentas ser mais exploradas e utilizadas no decorrer do tratamento como auxiliares na avaliação de sua eficácia.

Unitermos: terapêutica; radiografia panorâmica; diagnóstico.

#### **REFERENCES**

- 1. De Lange J, Van DA, Klip H. Incidence and disease-free survival after surgical therapy of central giant cell granulomas of the jaw in The Netherlands: 1990-1995. Head Neck. 2004; 26: 792-5.
- 2. Eisenbud L, Stern M, Rothenberg M, et al. Central giant cell granuloma of the jaws: experiences in the management of thirty-seven cases. J Oral Maxillofac Surg. 1988; 46:376-4.
- 3. Waldron CA, Shaffer WG. The central giant cell reparative granuloma of the jaws. An analysis of 38 cases. Am J Clin Pathol. 1966; 45: 437-47.
- 4. Cohen MA, Hertzanu Y. Radiologic features, including those seen with computed tomography, of central giant cell granuloma of the jaws. Oral Surg Oral Med Oral Pathol. 1988; 65: 255-61.
- 5. Austin LT, Dahlin DC, Royer RQ. Giant-cell reparative granuloma and related conditions affecting the jawbones. Oral Surg Oral Med Oral Pathol. 1959; 12: 1285-95.

- 6. Andersen L, Fejerskov O, Philipsen HP. Oral giant cell granulomas. A clinical and histological study of 129 new cases. Acta Pathol Microbiol Scand. 1973; 81: 606-16.
- 7. Auclair PL, Cuenin P, Kratochvil FJ, et al. A clinical and histomorphologic comparison of the central giant cell granuloma and the giant cell tumor. Oral Surg Oral Med Oral Pathol. 1988; 66: 197-208.
- 8. Whitaker SB, Waldron CA. Central giant cell lesions of the jaws. A clinical, radiologic, and histopathologic study. Oral Surg Oral Med Oral Pathol. 1993; 75: 199-208.
- 9. Kaban LB, Troulis MJ, Ebb D, et al. Antiangiogenic therapy with interferon alpha for giant cell lesions of the jaws. J Oral Maxillofac Surg. 2002; 60: 1103-11.
- 10. Harris M. Central giant cell granulomas of the jaws regress with calcitonin therapy. Br J Oral Maxillofac Surg. 1993; 31: 89-94.
- 11. De Lange J, Rosenberg AJ, van den Akker HP, et al. Treatment of central giant cell granuloma of the jaw with calcitonin. Int J Oral Maxillofac Surg. 1999; 28: 372-6.
- 12. O'Regan EM, Gibb DH, Odell EW. Rapid growth of giant cell granuloma in pregnancy treated with calcitonin. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001; 92: 532-8.
- 13. Pogrel MA. Calcitonin therapy for central giant cell granuloma. J Oral Maxillofac Surg. 2003; 61: 649-53.
- 14. Webb DJ, Brockbank J. Combined curettage and cryosurgical treatment for the aggressive "giant cell lesion" of the mandible. Int J Oral Maxillofac Surg. 1986; 15: 780-5.
- 15. Rajeevan NS, Soumithran CS. Intralesional corticosteroid injection for central giant cell granuloma. A case report. Int J Oral Maxillofac Surg. 1998; 27: 303-4.
- 16. Khafof A, Krempl G, Medina JE. Treatment of giant cell granuloma of the maxilla with intralesional injection of steroids. Head Neck. 2000; 22: 822-5.
- 17. Kurtz M, Mesa M, Alberto P. Treatment of a central giant cell lesion of the mandible with intralesional glucocorticosteroids. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001; 91: 636-7.
- 18. Carlos R, Sedano HO. Intralesional corticosteroids as an alternative treatment for central giant cell granuloma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002; 93:161-6.

- 19. Abdo EN, Alves LC, Rodrigues AS, et al. Treatment of a central giant cell granuloma with intralesional corticosteroid. Br J Oral Maxillofac Surg. 2005; 43: 74-6.
- 20. Nogueira RLM, Teixeira RC, Cavalcante RB, et al. Intralesional injection of triamcinolone hexacetonide as an alternative treatment for central giant-cell granuloma in 21 cases. Int J Oral Maxillofac Surg. 2010: 39: 1204-10.
- 21. Teixeira RC, Rubira CMF, Assis GF, et al. Radiological and histopathological evaluation of experimentally-induced periapical lesion in rats. J Appl Oral Sci. 2011; 19: 500-4.
- 22. Choung R, Kaban LB, Kozakewich H, et al. Central giant cell lesions of the jaws: a clinicopathologic study. J Oral Maxillofac Surg. 1986; 44: 708-13.
- 23. Kramer IRH, Pindborg JJ, Shear M. Histological typing of odontogenic tumours. 2 ed. Germany: Springer-Verlag; 1991. p. 256-61.
- 24. Kaffe I, Ardekian L, Taicher S, et al. Radiologic features of central giant cell granuloma of the jaws. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1996: 81: 720-6.
- 25. De Lange J, van den Akker HP. Clinical and radiological features of central giant-cell lesions of the jaw. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005; 99: 464-70.
- 26. Vered M, Buchner A, Dayan D. Immunohistochemical expression of glucocorticoid and calcitonin receptors as a tool for selecting therapeutic approach in central giant cell granuloma of the jawbones. J Oral Maxillofac Surg. 2006; 35: 756-60.
- 27. Rawashdehh MA, Bataineh AB, AL-Khateeb T. Long-term clinical and radiological outcomes of surgical management of central giant cell granuloma of the maxilla. Int J Oral Maxillofac Surg. 2006; 35: 60-6.
- 28. Ohki M, Okano T, Nakamura T. Factors determining the diagnostic accuracy of digitized conventional intraoral radiographs. Dentomaxillofac Radiol. 1994; 23: 77-82.
- 29. Fulton WA. A few scanning tips. USA. 2004.
- 30. Bataineh AB, AL-Khateeb T, Rawashdehh MA. The surgical treatment of central giant cell granuloma of the mandible. J Oral Maxillofac Surg. 2002; 60: 756-61.

#### CORRESPONDING AUTHOR

#### Israel Leal Cavalcante

Departamento de Odontologia; Universidade Federal do Rio Grande do Norte; Av. Senador Salgado Filho, 1787; Lagoa Nova; CEP: 59056-000; Natal-RN, Brasil; Phone/Fax: +55 (84) 3215-4138; e-mail: isrraelleal@hotmail.com.



This is an open-access article distributed under the terms of the Creative Commons Attribution License.