

https://dspace.org/

Cemento-osseous dysplasia: a retrospective clinico-pathological study

Benaessa, Mouna Mohamed Salim

2018

https://hdl.handle.net/10539/25264

Downloaded from a DSpace repository. https://dspace.org/



CEMENTO-OSSEOUS DYSPLASIA: A RETROSPECTIVE CLINICO-PATHOLOGICAL STUDY

Mouna Mohamed Benaessa

1454372

A research report submitted to the Faculty of Health sciences, University of the Witwatersrand, In conformity with the requirements for the degree of Master of Science in the branch of Oral Pathology

School of Oral Health Science, Faculty of Health Sciences

University of the Witwatersrand, South Africa

Johannesburg, 2018

DECLARATION

I, Mouna M Benaessa declare that this research report is my own work. It is being submitted for an MSc(Dent) degree in the branch of Oral Pathology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University. All the sources I have used or quoted have been indicated and acknowledged by complete references.

M.Benaessa

8th June 2018.

DEDICATION

To my mother, father and extended family for their support and encouragement.

I am heartily thankful to my supervisors, Dr. Sizakele P Ngwenya and Dr. Farzana Mahomed, for their invaluable assistance, guidance and support.

Abstract

Background:

Cemento-osseous dysplasia (COD) is a non-neoplastic fibro-osseous lesion which occurs in the tooth-bearing regions of the jaw bones. In many instances the diagnosis of COD is based on the distinctive clinical and radiographic features of this disease. Since the affected bone in COD progressively becomes poorly vascularized, dental prophylaxis is of paramount importance to prevent pulpal and periodontal infection which typically trigger sequestrum formation in the affected bone. The aim of this study was to determine the clinico-pathological characteristics of COD in a South African population sample and to relate this to findings in the literature.

Materials and methods:

The study comprised a retrospective record review of archived documentation of COD. The histopathology reports of patients diagnosed with COD over the period spanning 1996 to 2015 were reviewed from the files of the Department of Oral Pathology, School of Oral Health Sciences, University of the Witwatersrand, Johannesburg.

Results:

Of the 23, 288 specimens submitted for histopathological examination 237 (1.02%) cases of COD were found. The mean age of the patients were 53.4 years ± 14.2 years with a 93.2% female predilection. COD mainly affected the mandible (62.4%), followed by involvement of both the maxilla and the mandible (24.5%), and maxilla (13.1%). Of the 143 patients with known COD

subtypes florid COD predominated (65%) showing a clear trend of increasing with age, peaking in the 51-60 year age group and then decreasing thereafter. Cases of infected COD comprised 73.8% (174/237) of the COD study sample. Further 33% of all cases of chronic suppurative osteomyelitis (CSOM) in this study were seen in patients with COD. There was no significant association between any of the COD subtypes and CSOM ($p > 0.05$). Simple bone cysts presented as a complication of COD in 4.6% of cases.

Conclusion:

This study comprises the largest sample of COD cases thus far reported from South Africa. It showed a higher frequency of CSOM occurring as a complication of COD compared to earlier studies. No significant association was shown between any of the COD subtypes and CSOM.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my supervisors, Dr. Sizakele P Ngwenya and Dr. Farzana Mahomed who taught and guided me with the research. Thank you for your guidance, patience, insightful comments and continuous encouragement for my MSc study and research.

My deepest gratitude also goes to:

- The staff members of the Oral Pathology Department of the School of the Oral Health Sciences at the University of the Witwatersrand.
- To my family and colleagues for supporting me spiritually throughout my life.

Table of Contents

DECLARATION i

Abstract iii

Table of Contents vi

ABBREVIATIONS viii

LIST OF FIGURES ix

LIST OF TABLES x

CHAPTER 1.INTRODUCTION AND LITERATURE REVIEW 1

Introduction 1

Literature Review 2

1.1 Terminology and classification 2

1.2 Demographic Presentation 7

1.3 Clinical Presentation 9

CHAPTER 2.AIM AND OBJECTIVES 13

2.1 Aim 13

2.2 Objectives 13

CHAPTER 3.METHODOLOGY 14

3.1 Study design 14

3.2 Study material 14

3.3 Inclusion criteria 14

3.4 Exclusion criteria 14

3.5 Data collection 15

3.6 Statistical analysis 15

3.7 Ethical considerations 15

CHAPTER 4.RESULTS 16

4.1 Study sample 16

4.2 COD and Age 16

4.3 COD and Gender 16

4.4 COD and Site 17

4.5 Frequency of COD subtypes 17

4.6 COD subtypes and Age 18

4.7 COD subtypes and Gender 21
4.8 COD subtypes and Site 23
4.9 COD and Complications 25
4.10 Re-reported patients 28
CHAPTER 5.DISCUSSION 30
CHAPTER 6 42
6.1 Conclusions 42
6.2 Recommendations arising from this study 43
6.3 Limitations of this study 43
REFERENCES 44
Appendix A1 *- Permission from Head of Department of Oral Pathology* 53
Appendix A2 *- Permission from Head of School of Oral Health Sciences* 54
Appendix A3 *– Title Approval* 55
Appendix B *– Raw data* 56
Appendix C *– Re-reported patients during study period* 61
Appendix D *- Plagiarism Report* 62

ABBREVIATIONS

BFOL: Benign Fibro-Osseous Lesion

COD: Cemento-Osseous Dysplasia

CSOM: Chronic Suppurative Osteomyelitis

SBC: Simple Bone Cyst

ABC: Aneurysmal Bone Cyst

WHO: World Health Organisation

LIST OF FIGURES

Figure 1 : The relative frequency of the cemento-osseous dysplasia (COD) subtypes..... 18

Figure 2: The mean ages of patients under each subtypes of cemento-osseous dysplasia..... 19

Figure 3: The distribution of cemento-osseous dysplasia cases across the age groups 21

Figure 4:The proportion of male and female patients according to subtypes of cemento-osseous dysplasia 22

Figure 5: The Proportion of different cemento-osseous dysplasia subtypes that presented…..……23

Figure 6: The proportion of different cemento-osseous dysplasia (COD) subtypes that…….....24

Figure 7: The proportion of different cement-osseous dysplasia (COD) subtypes that.....…...24

LIST OF TABLES

Table 1 . WHO Classification of Odontogenic Tumours Jaw cysts and allied lesions, 1971 3

Table 2. WHO classification of Odontogenic Tumours, 1992 4

Table 3. WHO classification of Odontogenic Tumours, 2005 4

Table 4. WHO classification of Odontogenic Tumours, 2017 4

Table 5. Summary of literature findings on familial cemento-osseous dysplasia 6

Table 6.Review of literature on expansive osseous dysplasia 7

Table 7. Review of literature on male cases of cemento-osseous dysplasia (COD) 8

Table 8. The descriptive statistic of the cemento-osseous dysplasia (COD) study population and age (years) 16

Table 9. Site predilection of cemento-osseous dysplasia 17

Table 10. Relative frequency of the cemento-osseous dysplasia (COD) subtypes 17

Table 11. The age (in years) distribution of the cemento-osseous dysplasia (COD) subtypes 19

Table 12. The distribution of cases in the different subtypes of cemento-osseous dysplasia (COD) among patients in the different decades of life 20

Table 13. Cemento-osseous dysplasia (COD) subtypes in male patients related to age 22

Table 14. Comparison of infected and non-infected cemento-osseous dysplasia (COD) subtypes 25

Table 15. Chronic suppurative osteomyelitis (CSOM) in patients with and without cemento-osseous dysplasia (COD) 26

Table 16. Mean age of patients with infected cemento-osseous dysplasia (COD) and chronic suppurative osteomyelitis (CSOM) 26

Table 17. Site predilection of infected cemento-osseous dysplasia (COD) and chronic suppurative osteomyelitis (CSOM) 27

Table 18. Gender distribution of cemento-osseous dysplasia (COD) and Chronic suppurative osteomyelitis (CSOM) 27

Table 19. Logistic regression between chronic suppurative osteomyelitis (CSOM) and gender..... 27

Table 20. Comparison of simple bone cyst (SBC) associated with cemento-osseous dysplasia (COD) and unassociated with COD..... 28

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Introduction

Cemento-osseous dysplasia (COD) is defined as an idiopathic process which occurs in the tooth-bearing areas of the jaws (El-Naggar *et al*., 2017). Based on the extent of jaw involvement, COD has been subtyped into focal, periapical and florid forms; which all represent variants of the same pathologic process (EI-Naggar *et al*., 2017). Histologically, these lesions are characterised by the replacement of normal bone by fibrous tissue in which there is bone and cementum-like tissue (Abramovitch and Rice, 2016). COD shares these histological features with a diverse group of bone lesions which may present in the jaws and which are termed "benign fibro-osseous lesions" (Neville *et al*., 2015). In most published studies on COD, this jaw disease was lumped together with the other fibro-osseous lesions in particular with cemento-ossifying fibroma and fibrous dysplasia (Ogunsalu *et al*., 2001; Ali, 2011; Worawongvasu and Songkampol, 2010; Butt *et al*., 2012; Kolomvos *et al*., 2013; Netto *et al*., 2013; Lasisi *et al*., 2014; Muwazi and Kamulegeya, 2015; Sule *et al*., 2017). Further, whilst there are some local studies on COD, most of these focused on rare forms of presentation of COD, namely expansive osseous dysplasia (Noffke and Raubenheimer, 2011; Raubenheimer *et al*., 2016) and hereditary forms of COD (Coleman *et al*., 1996). The last clinico-pathological appraisal of COD in the South African context was published in 1992 (Ackermann and Altini, 1992). The purpose of this study is to provide an up to date report on the clinico-pathological features of COD in a South African population sample.

Literature Review

1.1 Terminology and classification

The term benign fibro-osseous lesion is a descriptive term for a group of conditions of the jaws characterised by the replacement of normal bone by fibrous tissue, metaplastic bone and cementum-like material (Abramovitch and Rice, 2016). This group includes developmental conditions such as fibrous dysplasia, reactive lesions such as COD and neoplasms such as ossifying fibroma (Ongole and Praveen, 2014). These lesions are grouped together because histologically they show replacement of the normal bone by fibrous connective tissue along with varying degrees of mineralisation (Abramovitch and Rice, 2016). The benign fibro-osseous lesions are notorious for their significant overlap in histological appearance. Often an accurate diagnosis of the lesion can only be made following careful correlation of the histological findings on the biopsy specimen with the clinical and radiological presentation (Neville *et al*., 2015).

COD is a non-neoplastic fibro-osseous lesion which occurs in the tooth-bearing regions of the jaw bones. As COD usually locates in close proximity to the apices of teeth, many accept that it originates from periodontal ligament tissue (Kawai *et al.,* 1999). In edentulous regions, authors considered that medullary bone around periodontal ligament tissue might be able to give arise to cementoid tissue as the osteoblastic lining of alveolar processes and the periodontal ligament are contiguous through Volkmann's canals (Kawai *et al*., 1999). The aetiology of COD is unknown. Some investigators suggest that COD represents a defect in alveolar bone remodeling that may be triggered by local and hormonal factors.

In the first World Health Organisation (WHO) classification of odontogenic tumours in 1971, four lesions referred to as "cementomas" were grouped together under the heading of "neoplasms and other tumours related to the odontogenic apparatus" (Pindborg *et al*., 1971). The "cementomas" comprised benign cementoblastoma, periapical cemental dysplasia, cementifying fibroma and gigantiform cementoma (Table 1). Fibrous dysplasia and ossifying fibroma were placed in the category of "neoplasms and other tumours related to bone" (Pindborg *et al*., 1971).

Table 1 . *WHO Classification of Odontogenic Tumours Jaw cysts and allied lesions, 1971*

I. Neoplasms and other tumours related to the odontogenic apparatus

Cementomas

a. Benign cementoblastoma (true cementoma)
b. Cementifying fibroma
c. Periapical cemental dysplasia
d. Gigantiform cementoma (familial multiple cementomas)

In the second WHO classification on odontogenic tumours in 1992, COD was placed in the group of non-neoplastic bone lesions. Under this title COD was sub-divided into periapical cemental dysplasia, florid COD (gigantiform cementoma, familial multiple cementomas) and other cemento-osseous dysplasias (Table 2) (Kramer *et al*., 1992).

Table 2*. WHO classification of Odontogenic Tumours, 1992*

Non-neoplastic bone lesions
Cemento-osseous dysplasia
a. Periapical cemental dysplasia
b. Florid cemento-osseous dysplasia (gigantiform cementoma, familial multiple cementoma)
c. Other cemento-osseous dysplasias

In the 2005 WHO classification of odontogenic tumors COD was placed under the category of "bone-related lesions" and was termed "osseous dysplasia" (Table 3) (Barnes *et al*., 2005).

Table 3*. WHO classification of Odontogenic Tumours, 2005*

Bone-related lesions
Osseous dysplasia
• Periapical osseous dysplasia
• Focal osseous dysplasia
• Florid osseous dysplasia
• Familial gigantiform cementoma

Recently, in the 2017 publication the WHO classified COD under the category of "fibro-osseous lesions" (El-Naggar *et al*., 2017) as shown in Table 4.

Table 4*. WHO classification of Odontogenic Tumours, 2017*

Fibro-osseous lesions
1. Familial gigantiform cementoma
2. Cemento-osseous dysplasia
• Periapical cemento-osseous dysplasia
• Focal cemento-osseous dysplasia
• Florid cemento-osseous dysplasia

All forms of COD have similar histopathological features characterised by a mixture of woven bone, irregular bony trabeculae, and cementum-like particles in a connective tissue stroma

(Owosho *et al*., 2013). Periapical COD appears as a single or multiple lesions in the anterior mandible in the periapical region of vital teeth (Speight and Carlos, 2006; Netto *et al*., 2013; El-Naggar *et al*., 2017). Individual lesions are rarely more than 1.0 cm in diameter. Lesions show an increasing degree of calcification with time, which appear as mixed radiopaque and radiolucent lesions with eventual completely radiopaque masses without bone expansion. Early radiolucent lesions may be misdiagnosed radiographically as a periapical abscess or a radicular cyst (Ongole and Praveen, 2014). Although focal COD may involve any site of the jaw, whether edentulous or not, most present as a single lesion smaller than 1.5 cm in diameter usually in the posterior mandible (Neville *et al.*, 2015). Radiographically, focal COD most commonly presents as a mixed radiolucent and radiopaque lesion with well-defined or slightly irregular borders (Neville and Albenesius, 1986). Florid COD occurs most commonly bilaterally and symmetrically in the mandible but may involve all four quadrants of the jaws (Speight and Carlos, 2006; El-Naggar *et al*., 2017). Florid COD may involve tooth-bearing areas of the jaws or edentulous alveolar ridges but is generally not associated with expansive cortical plates (Netto *et al*., 2013). The fourth subtype of COD, familial gigantiform cementoma (familial COD) is a rare condition characterised by early onset of multi-quadrant progressively expansile lesions that may become huge (El-Naggar *et al*., 2017). Autosomal dominant inheritance is demonstrated in some cases whereas other cases are sporadic (El-Naggar *et al*., 2017). A summary of the literature findings on familial COD is presented in Table 5.

Table 5*. Summary of literature findings on familial cemento-osseous dysplasia*

Author	No. of cases	Mean age (years)	Gender	Site
Sedano *et al*., 1982	10	40	4 M 6 F	NS
Young *et al*., 1989	11	6	3 M 8 F	Both jaws=1 NS=10
Oikarinen *et al*., 1991	3	19.6	2 M 1 F	Mandible=1 Both jaws=2
Coleman *et al*., 1996	3	18	1 M 2 F	Mandible=1 Both jaws=2
Hatori e*t al*., 2003	2	45.5	1 M 1 F	Both jaws=2
Sim *et al*., 2014	3	30.3	3 F	Both jaws=3
Thorawat *et al*.,2015	2	34.5	2 F	Both jaws=2
Kucukkurt *et al*., 2016	3	31.5	2 F 1 M	Both jaws=3
Summary	37	27.4	12 M 23 F	Both jaws=15 Mandible=2 NS=11

M=male; F=female; NS=not specified

The sporadic (non-familial) cases of COD that manifest with progressive jaw expansion are thought to represent a separate clinical subcategory of COD, which in the study by Raubenheimer *et al*. (2016) showed a female predominance and a mean age of 34.6 years. Unlike the familial form of the disease, which typically presents with multi-quadrant disease (Coleman *et al*., 1996), this variant of COD showed a predilection for the anterior mandible in the study by Noffke and Raubenheimer (2011) who proposed the term "expansive osseous dysplasia" for sporadic cases of COD that presents with gross expansion of the jaw. A case of expansive osseous dysplasia characterised by progressive increase in size and swelling of the affected posterior maxilla was

recently reported in a 46-year old female as a variant of COD that differs from the benign and usually asymptomatic COD (Singh *et al*., 2016) (Table 6).

Table 6*.Review of literature on expansive osseous dysplasia*

Author	No. of cases	Mean age (years)	Gender	Site
Noffke and Raubenheimer, 2011	8	44.6	1 M 7 F	Mandible=7 Both jaws=1
Raubenheimer *et al*., 2016	14	34.6	2 M 12 F	Maxilla=4 Mandible=10
Singh *et al*., 2014	1	46	1 F	Maxilla=1
Summary	23	41.7	3M 20F	Mandible=17 Maxilla=5 Both jaws=1

M=male; F=female

1.2 Demographic Presentation

Published reviews of COD are in general agreement that this condition shows a strong predilection for females (Kawai *et al*., 1999; MacDonald-Jankowski., 2004; Alsufyani and Lam, 2011). Neville and Albenesius (1986) reported prevalence rates of COD of 5.5% among African females over 21 years of age. In a Japanese study on COD by Kawai *et al*. (1999) forty-nine (91%) of the 54 cases were found in females and the average age was 49.4 years, while the age of male patients (17.1%) with COD ranged from 13 to 70 years. Cho *et al*. (2007) reported an incidence rate of COD in a Korean population of 0.31%, this figure increased to 1.1% among females over the age of 40 years. In the study by Alsufyani and Lam (2011) the majority of COD cases were also found in females who comprised 82.9% of their study sample with an age range of 13 to 73 years, while male patients (17.1%) with COD ranged from 13 to 70 years. Reports of COD in male patients are uncommon. A summary of the literature findings on COD in males is presented in Table 7.

Table 7*. Review of literature on male cases of cemento-osseous dysplasia (COD)*

Author	No of cases	Mean age	COD subtype
Kawai *et al*., 1999	5	64.6 years	NS
Ackermann and Altini, 1992	4	43.5 years	4 focal COD
Summerline and Tomich, 1994	24	NS	24 focal COD
Sule *et al*., 2017	1	NS	NS
Butt *et al*., 2012	1	NS	NS
Elbeshir and Alhadad, 2017	2	NS	2 florid COD
Worawongvasu and Sonkampol, 2010	4	NS	4 periapical COD
Alsufayni and Lam, 2011	20	40.1 years	NS
Owosho *et al*., 2013	2	53.9 years	1 periapical COD 1 focal COD
Pereira *et al*., 2016	1	NS	1 florid COD
Summary	64	50.5 years	3 florid COD 5 periapical COD 29 focal COD 4 NS

NS=not specified

According to the results of a systematic review by Owosho *et al*., (2013), of the 35 patients with COD, 33 (94.3%) were female with a predilection for individuals of African descent (32/35, 91.4%) while only three (8.6%) of the patients with COD were Caucasians. The peak age group of COD occurrence was the fifth and sixth decades of life (Owosho *et al*., 2013). Taken together, as far as demographic indices are concerned, COD has been reported predominantly in middle-aged to elderly women of African descent. The condition rarely affects Caucasians and Asians (Neville and Albenesius, 1986; MacDonald-Jankowski, 2003). Although COD mainly affects

people of African descent, not much has been reported about them as an entity from Africa. Further, African data on the prevalence of these lesions is equivocal. In a hospital-based study conducted in Nigeria over 22 years, only one (0.8%) case of florid COD was found among 121 benign fibro-osseous lesions of the jaws (Lasisi *et al*., 2014). Muwazi and Kamulegeya (2015) reported a prevalence of COD in Uganda of 10.9% with an age range from 6 to 69 years, while two (3.3%) cases of COD out of 60 benign fibro-osseous lesions were documented during a 5-year study in Northern Nigeria (Sule *et al*., 2017). In many of these studies COD subtyping was not performed. In a retrospective study on COD conducted in South Africa, 107 cases of COD were reported which comprised mainly focal COD (59%), while florid COD accounted for 12% of the COD cases (Ackermann and Altini, 1992).

1.3 Clinical Presentation

COD may be completely asymptomatic. In many cases the condition is discovered only when radiographs are taken for another objective (Hwang and Lee, 1987; Goncalves *et al*., 2005). In a systemic review of the literature, it was found that 64% of all focal COD cases were an incidental finding. Pain and swelling occurred at rates of 25% and 28% respectively (MacDonald-Jankowski, 2008). The exposure of sclerotic masses of COD might develop as result of progressive atrophy of the alveolar ridge under a dental prosthesis or following extraction of the adjacent teeth (Tonioli and Schindler, 2004; Goncalves *et al*., 2005). For the asymptomatic patient management consists of prophylaxis to prevent tooth loss and the development of periodontal disease is required to avoid the complication of bone infection.

Secondarily infected lesions show features of chronic suppurative osteomyelitis (Neville *et al*., 2015). In the study by Ackermann and Altini (1992); the most common presenting features were sequestration with ulceration of the overlying mucosa and symptoms of osteomyelitis such as pain, swelling and drainage of pus. For symptomatic cases sequestration of the sclerotic cementum and bone is required. The characteristic clinical manifestations of familial gigantiform COD are usually that of maxillary and mandibular swellings with associated facial asymmetry, tooth impaction, malposition of teeth and malocclusion (Ongole and Praveen, 2014).

In a study involving four countries and comprising South Africa, the United States of America, Brazil and Guatemala, 18 (36%) of 50 patients with florid COD presented with infection manifesting with symptoms of pain or swelling and purulent discharge (Pereira *et al*., 2016). Radiographically, the lesions of florid COD typically demonstrate a cotton-wool like appearance with large, irregular areas of calcification that may resemble Paget's disease of bone (MacDonald-Jankowski, 2003). Paget's disease of bone, however, also demonstrates a strong association with hypercementosis, cortical expansion, extragnathic and multiple bone involvement while COD is exclusively gnathic (White and Pharoah, 2014). More sharply defined radiolucent areas within the COD lesion have on surgical exploration proven in many instances to be simple bone cysts (SBCs) which may be single or multiple (Neville *et al*., 2015).

SBCs can be observed in association with benign fibro-osseous lesions such as COD and fibrous dysplasia (Neville *et al*., 2015; White and Pharoah, 2014). Melrose *et al.* (1976) were the first to observe the coexistence of COD and SBC in their series of 34 patients with florid COD. The SBCs

that appear in older individuals exhibit several clinico-pathological differences as compared to the SBCs that develop in children and adolescents. When associated with COD these show a female predilection, numerous radiolucent lesions and the simultaneous presence of radiopaque lesions in the jaw or hypercementosis (Horner and Forman, 1988; Mahomed *et al*., 2005; Saito *et al*., 1992). In the study by Alsufyani and Lam (2011) out of 118 COD cases, 10 cases of periapical COD and 5 cases of florid COD were accompanied by one or more SBCs. By contrast, only one case was observed with SBC change in a series of 47 patients with florid COD in the study by Elbeshir and Alhadad (2017). The connection between COD and the SBC is not completely clear. Suei *et al* (2007) reported on 132 cases of SBC of the jaws. These authors found a 75% recurrence rate for SBC cases with COD lesions and hence suggested that those cases of SBC with COD lesions have a high risk of recurrence (Suei *et al*., 2007). The pathogenesis of SBC formation in COD is postulated to be due to venous blocking and interference of interstitial fluid drainage (Neville *et al*., 2015). In areas of rapidly remodeling spongy bone, as in the jaws, this may advance to the development of the SBCs (Mupparaou *et al.,* 2005). The SBC that presents in the absence of COD tends to heal better after surgical treatment than those associated with COD (MacDonald-Jankowski, 2004).

A more common, clinically significant problem for patients with COD is chronic suppurative osteomyelitis (CSOM). The lesions of COD tend to be sclerotic, hypovascular and highly susceptible to secondary infection (Neville *et al*., 2015). CSOM is a multifactorial disease of bone, caused primarily by infection of the jaw by oral micro-organisms (Aitasalo *et al*., 1998). The source of infection is often odontogenic such as from a dental or periodontal abscess or following dental extraction or trauma (Yeoh *et al*., 2005; Daramola and Ajagbe, 1982). In a

systemic review of CSOM, Koorbusch *et al* (1992) cited that the most prevalent causes of osteomyelitis of the jaws as odontogenic (dental infection-related) or traumatic (fracture-related) in nature. In a recent study, Malik and Singh (2014) noted in their series of 21 cases of CSOM that the most common cause was odontogenic infections (91.5%), which differs from the findings of Kim and Jang (2001) who observed that CSOM had an odontogenic cause in only 38.5% of their cases. Furthermore, other precipitating factors that are demonstrated in CSOM include the formation of avascular bone such as in osteopetrosis, Paget's disease of bone, irradiated bone and osseous dysplasia (Kim and Jang, 2001; Yeoh *et al*., 2005; Koorbusch *et al*., 1992). The prevalence of secondary infection in COD lesions of the jaw varies from 4% (Netto *et al*., 2013) to 78.7% (Elbeshir and Alhadad, 2017). Ackermann and Altini (1992) reported infection and sequestration in 54% of cases in their retrospective histopathological review of COD. In most published reports, florid COD was the subtype most commonly complicated by osteomyelitis (Netto *et al*., 2013; Owosho *et al*., 2013; Mawazi and Akamulegeya, 2015; Elbeshir and Alhadad, 2017). In the study by Alsufyani and Lam (2011), 13 (11.0%) cases of CSOM represented COD lesions with secondary CSOM. Of the 13 cases, there were six cases of florid COD and seven cases of periapical COD (Alsufyani and Lam, 2011). The frequency of CSOM occurring secondary to COD in the South African population has, however, not yet been studied.

CHAPTER 2

AIM AND OBJECTIVES

2.1 Aim

The aim of this study was to determine the clinico-pathological characteristics of cemento-osseous dysplasia diagnosed at the Department of Oral Pathology, School of Oral Health Sciences, University of the Witwatersrand, Johannesburg and to relate this to the current literature.

2.2 Objectives

1. To determine the relative frequency of histologically confirmed cemento-osseous dysplasia in a South African sample.
2. To determine the age, gender and site distribution of cemento-osseous dysplasia.
3. To identify the subtypes of cemento-osseous dysplasia.
4. To determine the relative frequency of chronic suppurative osteomyelitis presenting as a complication of cemento-osseous dysplasia.
5. To determine the relative frequency of simple bone cyst presenting as a complication of cemento-osseous dysplasia.

CHAPTER 3

METHODOLOGY

3.1 Study design

This study comprised a retrospective record review of archived documentation of COD.

3.2 Study material

The histopathology reports of patients diagnosed with COD over the period spanning 1996 to 2015 were extracted from the files of the Department of Oral Pathology, School of Oral Health Sciences, University of the Witwatersrand, Johannesburg.

3.3 Inclusion criteria

All cases with a histologically confirmed diagnosis of COD including focal, periapical, florid, expansive and familial forms of COD. The histopathology reports of all cases of chronic suppurative osteomyelitis (CSOM) and simple bone cyst (SBC) were also retrieved for the study period 1996 to 2015.

3.4 Exclusion criteria

Cases where a definitive diagnosis of COD could not be rendered either due to inadequate biopsy material or due to inadequate clinical and radiological information that is required for clinico-pathological correlation and diagnosis.

3.5 Data collection

Information on the patient's age and gender, site distribution of COD, the COD subtype, the presence of CSOM and SBC presenting as a complication of COD were recorded.

3.6 Statistical analysis

The relative frequency of histologically diagnosed cases of COD was determined by ascertaining the total number of histopathology cases accessioned during the study period. Descriptive statistics were carried out for the variables age, gender and site of lesion/s. Means and standard deviations were used for continuous variables while proportions and graphs were used for categorical variables. The frequencies of the various COD subtypes, COD with secondary osteomyelitis and COD with SBC change were analysed and expressed in tabular and graphic format. Statistically significant differences in categorical variables were assessed using the Fischer's exact and Chi-square tests. *P*-values of < 0.05 were regarded as significant.

3.7 Ethical considerations

Ethical clearance was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (Appendix A). Patients' confidentiality were protected by allocating study case numbers to the histopathology reports and removing personal identifiers. Permission to conduct the study was granted by the Head of Department of Oral Pathology (Appendix A1), Head of School of Oral Health Sciences (Appendix A2) and Title Approval for this study was also obtained (Appendix A3).

CHAPTER 4

RESULTS

4.1 Study sample

In this study within the period of 1996 to 2015, there were 23, 288 submissions of tissue specimens to the Oral Pathology department, out of which a histological diagnosis of COD was reported in 237 (1.02%) cases. There were 355 cases of CSOM and 11 cases of SBC not associated with COD.

4.2 COD and Age

Of the 237 COD patients their ages were known for all except five patients. The mean age of the 232 patients diagnosed with COD in this study was 53.4 years (Table 8).

Table 8*. The descriptive statistic of the cemento-osseous dysplasia (COD) study population and age (years)*

COD	n	Mean (SD)	Median	Min	Max
Total	232	53.4 (14.2)	53.5	9	87

4.3 COD and Gender

Of the 237 patients, 220 (93.2%) were female, and their ages ranged between 9 and 87 years (mean ± standard deviation 54.3 ± 13.6 years). The 16 (6.8%) male patients had an age range of 11 to 70 years (mean ± standard deviation 41.6 ± 16.7 years). Gender was not known in one case (Appendix B).

4.4 COD and Site

Site of the COD lesion/s was known for 229 cases while in 8 cases the site of the lesion was not specified. The mandible was far more commonly affected than the maxilla with 143 (62.4%) of the cases presenting in the lower jaw while only 30 (13.1%) cases presented in the maxilla. In 56 (24.5%) cases both jaws were affected (Table 9).

Table 9*. Site predilection of cemento-osseous dysplasia*

Number of COD cases with known affected site/s	Mandible	Maxilla	Both jaws
229	143	30	56

4.5 Frequency of COD subtypes

Based on the radiographic findings provided with the biopsy sample, the COD subtype was documented in the histopathology report in 143 cases. The relative frequencies of the COD subtypes are presented in Table 10 and in Figure 1. Five types of COD were identified with florid COD being the most prevalent (93 cases), followed by focal COD (24 cases), periapical (16 cases), expansive (6 cases) and familial / hereditary COD (4 cases). The COD subtype could not be determined from the histopathology reports in 94 cases.

Table 10*. Relative frequency of the cemento-osseous dysplasia (COD) subtypes*

COD subtype	Frequency (n)	%
Florid	93	65.0
Focal	24	16.8
Periapical	16	11.2
Expansive	6	4.2
Familial	4	2.8
Total	143	100

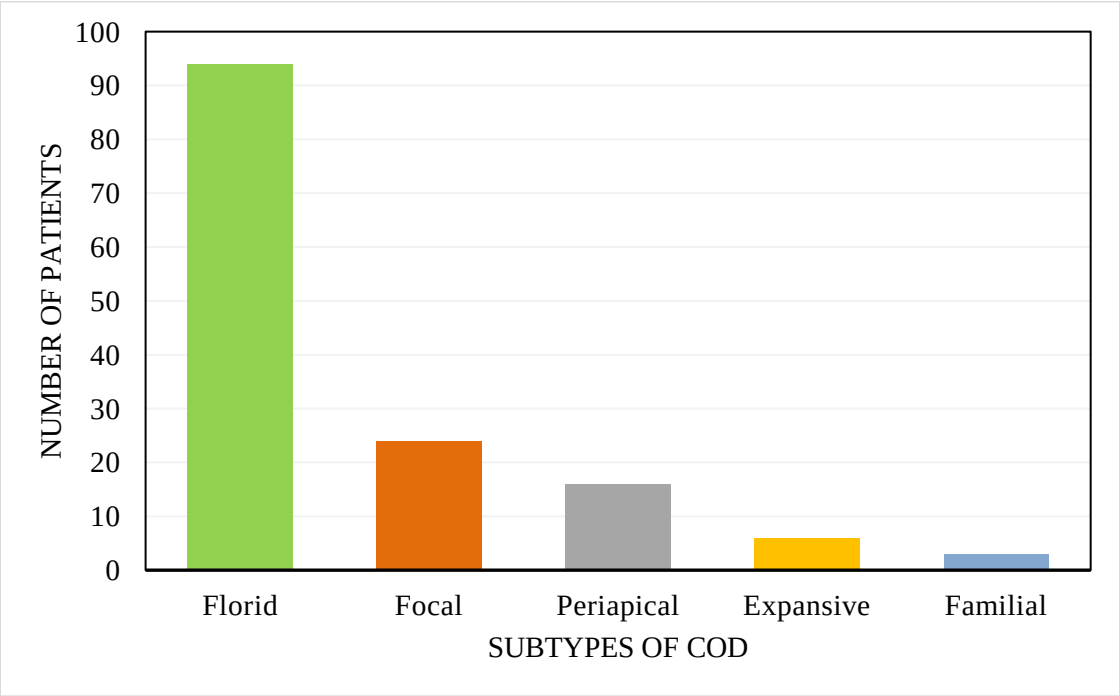


Figure 1 *: The relative frequency of the cemento-osseous dysplasia (COD) subtypes*

4.6 COD subtypes and Age

Of the 143 patients with known COD subtypes their ages were known for all except three patients; one patient with focal COD, one with florid COD and one with familial COD (Appendix B). The age distribution of the remaining 140 patients is presented in Table 11 and in Figure 2. Periapical COD (57.1 ± 16.6 years), florid COD (53.5 ± 13.0 years) and focal COD (51.2 ± 13.3 years) appeared to be more prevalent in older people. Expansive COD (42.3 ± 10.4 years) was common in the middle-aged while familial COD presented most commonly in young patients (29.7 ± 19 years).

Table 11. *The age (in years) distribution of the cemento-osseous dysplasia (COD) subtypes*

COD subtype	n	Mean (SD)	Median	Min	Max
Florid	92	53.5 (13.0)	53.0	9	85
Focal	23	51.2 (13.3)	54.0	28	78
Periapical	16	57.1 (16.6)	56.0	30	87
Expansive	6	42.3 (10.4)	42.5	30	55
Familial	3	29.7 (19.0)	20.0	11	50
Total	140				

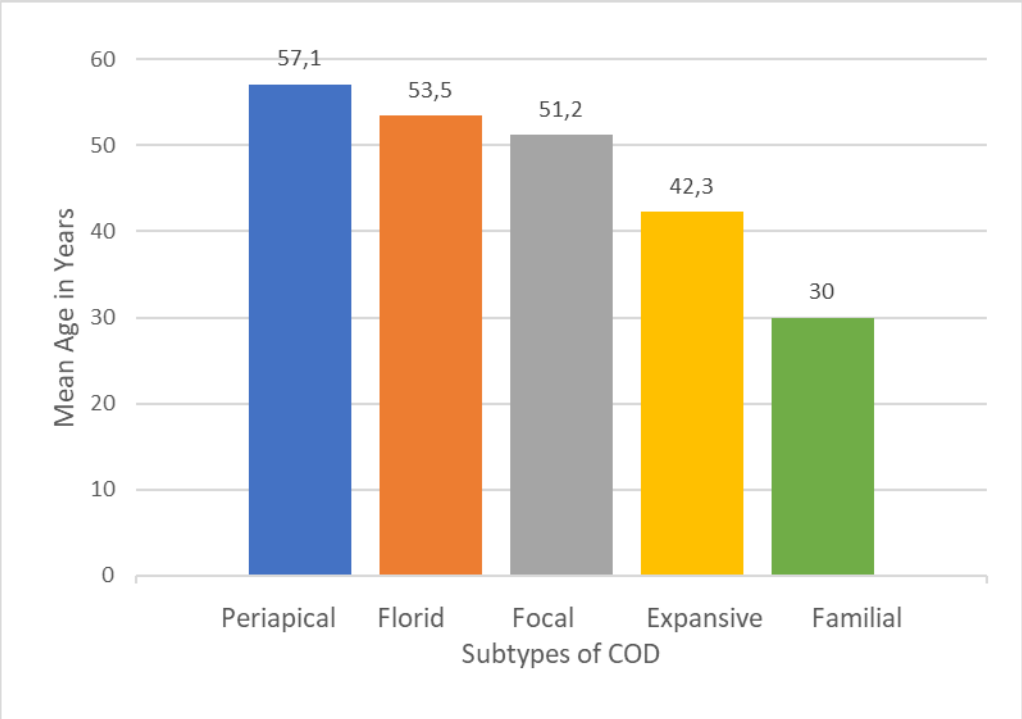


Figure 2: *The mean ages of patients under each subtypes of cemento-osseous dysplasia (COD)*

The age distribution of the COD subtypes was further subdivided into nine age groups (Table 12). It is evident from Figure 3 below that the cases of COD increased with age to about the sixth decade of life and then started decreasing thereafter. The occurrence of florid COD cases showed a clear trend of increasing with age, peaking in the 51-60 year age group and then decreasing thereafter. The other subtypes of COD showed no clear trends of decreasing as there were fewer cases. The average age of the patients was highest in patients with periapical COD (57.1 ± 16.6) followed by those with florid COD (53.5 ± 13.0) years, focal COD (51.2 ± 13.3), expansive COD (42.3 ± 10.4) and lastly those with familial COD with an average age of 29.7 ± 19 years.

Table 12*. The distribution of cases in the different subtypes of cemento-osseous dysplasia (COD) among patients in the different decades of life*

Age Group	Florid COD	Focal COD	Periapical COD	Expansive COD	Familial COD	Total
< 10 years	1	0	0	0	0	1
11 - 20 years	0	0	0	0	1	1
21 - 30 years	4	1	1	1	1	8
31 - 40 years	7	5	2	2	0	16
41 - 50 years	22	4	4	1	1	32
51 - 60 years	31	7	1	2	0	41
61 - 70 years	19	5	5	0	0	29
71 - 80 years	6	1	2	0	0	9
>80 years	2	0	1	0	0	3
Total	92	23	16	6	3	140

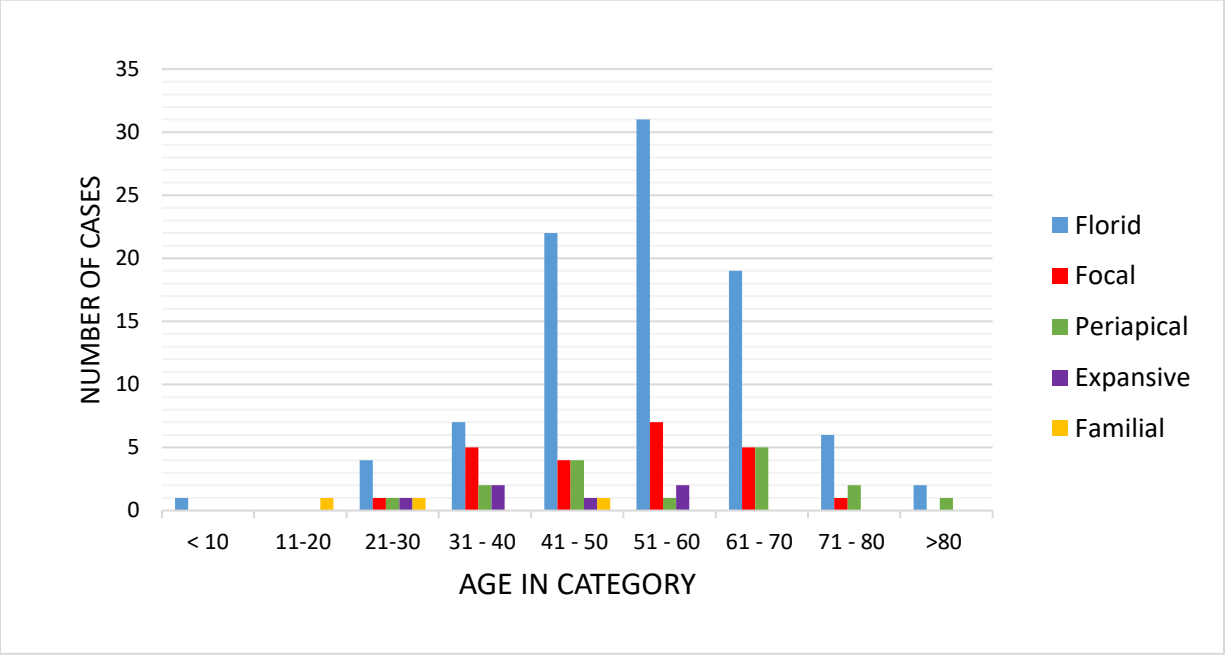


Figure 3: *The distribution of cemento-osseous dysplasia cases across the age groups*

4.7 COD subtypes and Gender

Females made the higher percentage (93.2%) than males (6.8%) for florid, focal, periapical and expansive COD (Figure 4). Of the four patients with familial COD, three were females while the gender was not known in one case (Appendix B). Of the 16 cases of COD in males, the COD subtype was not known in six cases. Of the 10 cases that were subtyped, there were three cases of florid COD, three cases of focal COD, one case of familial COD, one periapical COD and two cases of expansive COD (Table 13).

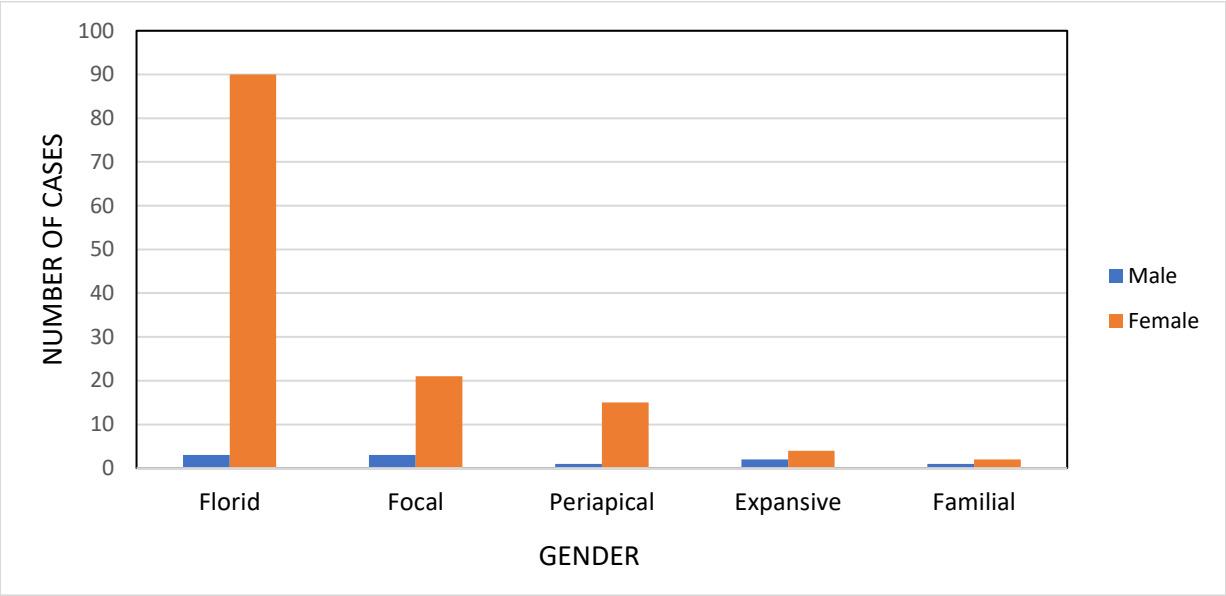


Figure 4*:The proportion of male and female patients according to subtypes of cemento-osseous dysplasia*

Table 13*. Cemento-osseous dysplasia (COD) subtypes in male patients related to age*

Age (years)	**COD subtype**
11	Familial
25	Not specified
27	Not specified
29	Not specified
30	Expansive
30	Florid
31	Florid
37	Not specified
46	Expansive
46	Not specified
48	Not specified
54	Focal
56	Focal
59	Florid
67	Focal
70	Periapical

4.8 COD subtypes and Site

The relative frequency of occurrence of the five COD subtypes in the mandible is depicted in Figure 5. Slightly more than half of all the COD cases that presented in the mandible were of the florid type; followed by focal COD, periapical COD, expansive and familial COD.

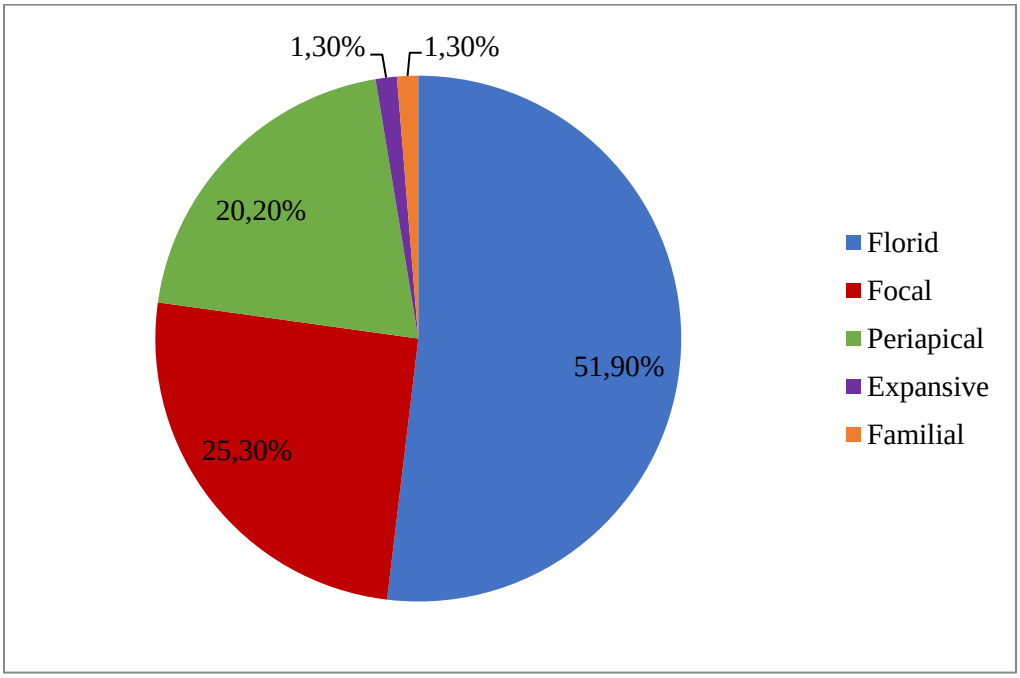


Figure 5: *The proportion of different cemento-osseous dysplasia subtypes that presented in the mandible*

When both the jaws were affected by COD, florid COD comprised 89.2% of the cases. Three of the six cases of expansive COD affected both jaws, while three of the four familial COD cases also affected both jaws at the time of diagnosis (Figure 6).

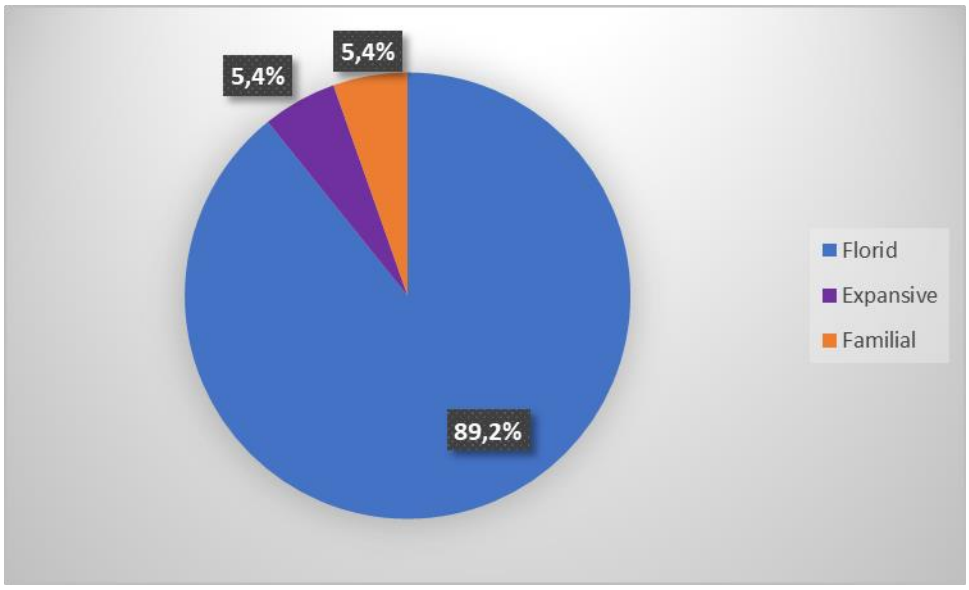


***Figure 6** : The proportion of different cemento-osseous dysplasia (COD) subtypes that presented in both jaws*

The fewest number of COD cases were seen in the maxilla (n=30), however, when affected focal COD was the most commonly encountered COD subtype in the maxilla followed by florid and expansive COD (Figure 7).

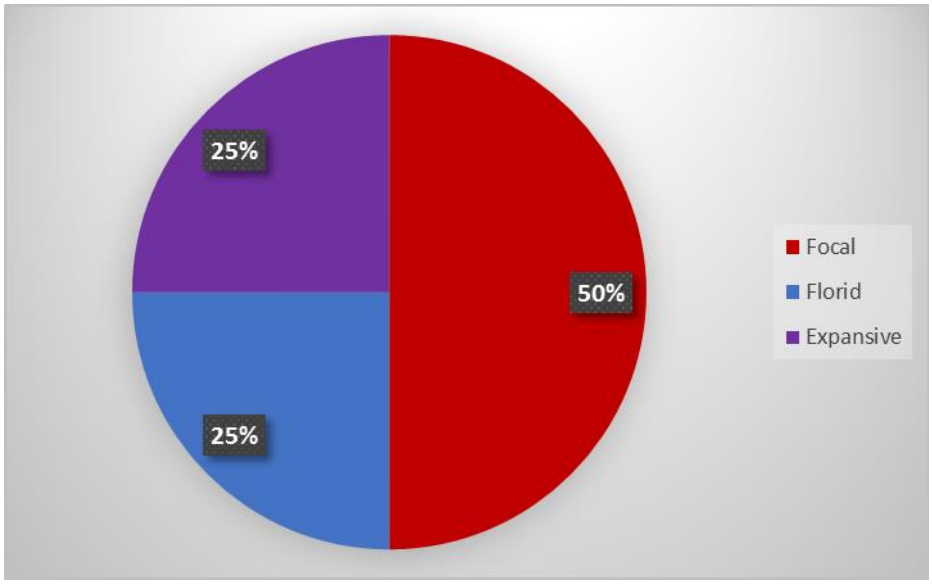


***Figure 7**: The proportion of different cemento-osseous dysplasia (COD) subtypes that presented in the maxilla*

4.9 COD and Complications

Of the 237 COD cases in this study, 174 (73.4%) cases showed concomitant features of COD and chronic suppurative osteomyelitis on biopsy. The latter cases represented cases of COD with secondary osteomyelitis referred to as infected COD in this study, while the remaining 63 cases represented cases of non-infected COD. Of these 11 cases were associated with simple bone cysts while one case showed secondary aneurysmal bone cyst change. Of the 174 infected COD cases, the COD subtype was known in 101 cases while in the 63 cases of non-infected COD the COD subtype was known in 42 cases (Appendix B).

The COD subtypes were statistically analysed to determine if any particular COD subtype was associated with a greater likelihood of infection (Table 14).

Table 14*. Comparison of infected and non-infected cemento-osseous dysplasia (COD) subtypes*

COD subtype	Infected COD	Non-infected COD	Fischer's exact test (p value)
Florid	72	21	0.1
Focal	15	9	
Periapical	10	6	
Expansive	2	4	
Familial	2	2	

Although most (72/101; 71.3%) cases of infected COD were of the florid subtype, florid COD was not significantly more likely to be associated with infection than the other COD subtypes (Table 14). The Fischer's exact test showed no significant association between any of the COD subtypes and infection ($p > 0.05$).

During the period of this study, there were 355 cases with a histologically confirmed diagnosis of chronic suppurative osteomyelitis (CSOM) without features of COD, bringing the total sample

size of all cases of CSOM, i.e. CSOM with COD (infected COD) and CSOM without COD to 529 cases (Table 15).

Table 15*. Chronic suppurative osteomyelitis (CSOM) in patients with and without cemento-osseous dysplasia (COD)*

CSOM	**Number of cases**
Total sample size of all cases of CSOM	529
CSOM with COD (infected COD)	174
CSOM without COD	355

It can be deduced from Table 15 that 33% of all cases of CSOM in this study represented cases of infected COD.

The mean age of patients diagnosed with CSOM without features of COD was 42.8 years (Table 16). The Student t-test showed that patients diagnosed with infected COD have a significantly higher mean age than patients diagnosed with CSOM without concomitant COD ($p < 0.05$; Table 16).

Table 16*. Mean age of patients with infected cemento-osseous dysplasia (COD) and chronic suppurative osteomyelitis (CSOM)*

Infected COD (mean age)	**CSOM (mean age)**	**T**	***p*-value**
53.4 years	42.8 years	8.77	0.00

Using Chi-square test for a measure of association between the diagnosis and the site of the lesion, there was a significant association ($p < 0.05$) as shown in Table 17.

Table 17*. Site predilection of infected cemento-osseous dysplasia (COD) and chronic suppurative osteomyelitis (CSOM)*

Site	**Infected COD**	**CSOM**	**X^2**	***p*-value**
Mandible	108	274	70.07	0.00
Maxilla	17	58		
Both	41	6		

Both infected COD and CSOM significantly more commonly affected the mandible than the maxilla or both jaws.

Table 18. *Gender distribution of cemento-osseous dysplasia (COD) and Chronic suppurative osteomyelitis (CSOM)*

Gender	**Infected COD**	**CSOM**	**X^2**	***p*-value**
Male	11	220	148.66	0.00
Female	162	134		

Using Chi-square test for a measure of association between the diagnosis and the gender of the patient, there was a significant association ($p < 0.05$) as shown in Table 18. CSOM was significantly more common in males while with infected COD females significantly outnumbered males. Further analysis using binary logistic regression as shown in Table 19 was done to determine the dimension of association between CSOM and categorical variable of gender.

Table 19*. Logistic regression between chronic suppurative osteomyelitis (CSOM) and gender*

Gender	**OR**	**95%CI**		
		Lower	Upper	*p*-value
Female	Ref	Ref	Ref	Ref
Male	22.64	11.82	43.38	0.00

As show in Table 19, the odds of a male being diagnosed with CSOM not associated with COD is significantly 22.64 times more likely than the female.

Eleven cases of COD were associated with simple bone cyst (SBC), while over the same study period there were an equal number of cases of SBC without associated COD. The mean age, gender and site distributions of these cases are presented in Table 20.

Table 20*. Comparison of simple bone cyst (SBC) associated with cemento-osseous dysplasia (COD) and unassociated with COD*

	Simple bone cyst	
	Associated with COD	**Unassociated with COD**
Number of cases	11	11
Mean age	49.5 years	26 years
Gender	Males = 0; Females = 11	Males = 4; Females = 7
Affected site	Mandible = 7; Maxilla = 1; Both jaws = 3	Mandible = 9; Maxilla = 2

SBC presented as a complication of COD in five cases of florid COD, (5/93; 5.3%), 3 cases of periapical COD (3/16; 18.8%) and in one case of expansive COD (1/6; 16.7%) while the COD subtype was not specified in the remaining two cases.

4.10 Re-reported patients

Multiple surgical specimens were received from 20 patients who re-presented for treatment during the study period (Appendix C). The average period from the initial patient presentation to when they re-reported was 23.2 months (range = 1 – 120 months). Of these; 15 patients required additional surgical debridement of COD lesions that were already infected at their initial

presentations. Four of the 14 patients with recurrent sepsis underwent three surgical debridement procedures during the follow-up period while one patient underwent a total of eight surgical debridement procedures during the follow-up period. Two patients developed complications of SBC. One patient with infected COD presented *10 years* later with a secondary aneurysmal bone cyst in the affected jaw while one patient with expansive COD was treated by a hemimaxillectomy.

CHAPTER 5

DISCUSSION

There are few published studies conducted in South Africa on the relative frequency of COD. Most local studies on COD focused only on rare forms of presentation of COD (Thompson and Altini, 1989; Coleman *et al*., 1996; Noffke and Raubenheimer, 2011; Raubenheimer *et al*., 2016). The last South African study on the clinico-pathological features of COD was published in 1992 (Ackermann and Altini, 1992). This study incorporated COD into a spectrum of other lesions previously termed "The Cementomas" (Ackermann and Altini, 1992). Hence an update of the clinico-pathological features of COD according to the 2017 WHO classification of COD (El-Naggar *et al*., 2017) and in the South African context formed the basis of this study.

COD represented 1.02% of the total number of histologically diagnosed cases over a 20-year period in the Department Oral Pathology at the University of the Witwatersrand, constituting a total study sample of 237 cases of COD. Owosho *et al*. (2013), reported 35 cases of COD over a six-year period in western Pennsylvania patients based on histopathological reports, clinical records and radiographs. African studies on the prevalence of COD are infrequent. Butt *et al*, (2012) noted 18 cases of COD out of 180 bone related jaw lesions in Kenya over 19 years. In a recent study, over a 5-year period, at Mulago Hospital in Uganda, the authors reported 17 cases of COD out of 155 fibro-osseous lesions (Muwazi and Kamulegeya, 2015). Another very recent African hospital-based in Northern Nigeria reported only two cases of COD out of 60 fibro-osseous lesions of the jaws over a 5-year period (Sule *et al*., 2017).

In the South African population, Thompson and Altini (1989) reported 28 cases of florid COD over a 20-year period under the old term "familial gigantiform cementoma" (Thompson and Altini, 1989) while Ackermann and Altini (1992) described 127 cases of COD in their clinico-pathological appraisal of "the cementomas" (Ackermann and Altini, 1992).

In the present study, the mean age at diagnosis of COD was 53.4 years, which is comparable with most other studies. The mean age at diagnosis of COD was 53.9 years in Western Pennsylvania patients (Owosho *et al*., 2013), 50.8 years in Japanese patients (Kawai *et al*., 1999), 51.9 years in Kenyan patients (Butt *et al.*, 2012) and 48.5 years in Ugandan patients *(*Muwazi and Kamulegeya, 2015). The age range of the patients in this study was 9-87 years which is comparable with the 6-69 year age range in a Ugandan study (Muwazi and Kamulegeya, 2015). The majority of the 237 COD subjects in this study were females 220 (93.2%) with a peak incidence in the sixth decade, a finding that corresponds with most published work on COD *(*Cho *et al.*, 2007; Alsufyani and Lam, 2011). A similar finding was reported in an earlier South African study where 96% of COD cases affected females in the fifth and sixth decades of life (Ackermann and Altini, 1992). In a 19-year audit, Butt *et al*, (2012) reported 17 (94%) cases of COD in females and one case (5.5%) in a male patient, while all COD patients in a Ugandan study were females (Muwazi and Kamulegeya, 2015). COD is prevalent in middle-aged women of African descent. This may suggest that X chromosome-linked and other genetic factors acting in concert with environmental factors are involved in the cause. Although the average age in women is generally coincident with the onset of menopause and is thought to be related to hormonal changes, the absence of gynaecological histories make this hypothesis untenable until clearer evidence is confirmed (MacDonald-Jankowski, 2004; MacDonald-Jankowski, 2008; Eversole *et al*., 2008; Kawai *et al*., 1999).

In this study COD showed a low prevalence in males, which is in accordance with published evidence. Analysis of the literature reveals less than 70 cases of COD reported in males, with the prevalence in males ranging from 1.2-10.9%. The mean age reported at diagnosis of COD in males in studies outside Africa is 52.9 years (Kawai *et al*., 1999; Alsufyani and Lam, 2011; Owosho *et al*., 2013). An interesting observation from this study was that COD presented a decade earlier in males (41.6 years) compared to the females (54.3 years) in this study and also a decade earlier than the mean age reported for males in non-African studies (Kawai *et al*., 1999; Alsufyani and Lam, 2011; Owosho *et al*., 2013). This observation is, however, not dissimilar to the findings of an earlier South African study on COD (Ackermann and Altini, 1992). The reason for the relatively earlier age at diagnosis for COD in South African male patients is not known, but may allude to a complex interplay between genetic and environmental factors in the development of this disease. Analysis of our male series showed five different COD subtypes, three cases of florid COD, three of focal COD, two cases of expansive COD and one case each of hereditary and periapical COD. The COD subtypes being unknown in the remaining six cases. The literature findings suggest that focal COD outnumbers the other COD subtypes in males accounting for 45.3% of all the COD cases reported in males, followed by the hereditary form of the disease which represents 21% of the reported cases in males (Kawai *et al*., 1999; Ackermann and Altini, 1992; Summerline and Tomich, 1994; Worawongvasu and Sonkampol, 2010; Alsufayni and Lam, 2011; Butt *et al*., 2012; Owosho *et al*., 2013; Pereira et al., 2016; Elbeshir and Alhadad,2017; Sule *et al*.,2017).

The mandible was the affected site in 62.4% of cases and the maxilla in 13.1% of cases. These findings are in agreement with most reports available in the literature. Altini and Ackermann (1992) noted the preponderance of the mandible in nearly 78% of cases of COD. Further, Owosho *et al*, (2013) and Worawongvasu and Songkampol (2010) also reported most COD cases in the mandible. Several reasons have been postulated for the mandibular predilection in COD, these largely attributing to the difference in bone composition between the maxilla and the mandible (Jerjes *et al*., 2005). The mandible has a higher mineral density and is less vascular than the maxilla. The affected bone in COD undergoes changes from normal vascular bone into an avascular cementum-like lesion (Jerjes *et al*., 2005). However, the aetiology of this change seen in the bone in COD continues to remain uncertain.

Of the 237 cases of histologically confirmed COD cases during the 20-year study period, adequate radiographic material allowing for the diagnosis of COD to be subtyped, was provided with 143 biopsy samples. The most frequent COD subtype in the present study was florid COD (65%), with a slightly higher frequency compared to studies from Korea, Brazil and Western Pennsylvania where the florid subtypes constituted 48.5% (Cho *et al*., 2007*),* 45.4% (Netto *et al*., 2013) and 48.6% (Owosho *et al*., 2013) of the COD cases respectively. This contrasts with the rates in series involving Ugandan, Nigerian and Thai populations, where florid COD respectively accounted for 10.3% (Muwazi and Kamulegeya, 2015), 0.8% (Lasisi *et al*., 2014) and 0.8% (Worawongvasu and Songkampol, 2010) of COD cases. Fun-Chee and Jinn-Fei (1989) reported a 11% prevalence of the florid subtype in 79 Oriental subjects with COD. In this study, the mean age of patients with florid COD was 53.5 years, which is similar to findings in Jamaican (52.5 years) (Muwazi and Kamulegeya, 2015), Ugandan (50.3 years) (Ogunsalu and Mile, 2005) and

systematic review studies (49 years) (MacDonald-Jankowski, 2003). Regarding gender and florid COD, females comprised 90 (96.7%) cases of the current series. This is also in accordance with the figures reported in Brazil (95%) (Netto *et al*., 2013), in systematic review studies (98%) (MacDonald Jankowski, 2003) and in an international collaborative study on florid COD (96.2%) (Pereira *et al*., 2016). Florid COD was seen in only three (3.2%) male patients in this study. Also only one male was reported by Melrose *et al.* (1976) in a series of 34 patients with florid COD. An international collaborative study on florid COD also reported only a single case in a male patient out of 100 cases of COD (Pereira *et al.*, 2016). Similarly, a study from Sudan reported two males (4.3%) out of 47 patients with florid COD (Elbeshir and Alhadad, 2017). Although florid COD has a high predilection for the mandible (MacDonald-Jankowski, 2003) in this study the majority (89.2%) of florid COD cases affected both the mandible and the maxilla while in the study by Pereira *et al* (2016), both jaws were affected in 53.7% of cases.

In the present study, focal COD was the second most frequent COD subtype (16.8%). Studies reported in Brazilian (12.6%) (Netto *et al*., 2013) and Pennsylvanian (14.3%) (Owosho *et al*., 2013) subjects yielded similar findings, whereas in other studies focal COD constituted 59% (Ackermann and Altini, 1992), 33% (Kawai *et al*., 1999) and 51.5% (Cho *et al*., 2007) of the COD cases respectively. Focal COD may occur at any age and all ethnic groups, but is reportedly more common in middle-aged subjects of African or Asian descent (Galgano *et al*., 2003). In this appraisal, focal COD was seen with greater frequency in females (95.8%) with a mean age of 51.2 years. Some authors report mean ages for focal COD slightly younger than this result; at 37.6 years (Summerlin and Tomich, 1994) and 45.9 years (Netto *et al*., 2013) respectively. Although focal COD showed a predilection for the mandible in some studies (MacDonald-Jankowski, 2008;

Summerlin and Tomich, 1994; Netto *et al*., 2013), there was an almost equal distribution of focal COD cases in the mandible and the maxilla.

The third most common COD subtype in this study was periapical COD; which represented 11.2% of the COD cases, a frequency that is higher than in Jamaican and Thai series with reported frequencies of 3.4%, and 3.3% respectively (Ogunsalu *et al*., 2001; Worawongvasu and Songkampol, 2010), but lower than studies reported by Owosho *et al* (2013) and Alsufyani and Lam (2011) in which periapical COD was found in 13 (37.1%) of 35 cases of COD (Owosho *et al*., 2013) and in 93 (78.8%) of 118 cases of COD (Alsufyani and Lam, 2011). A radiographic study conducted by Stafne (1934) in a sample of 10,000 cases revealed a prevalence of 0.24% for periapical COD while Neville and Albenesius (1986) reported a prevalence of 5.9% for periapical COD. In a 6-year retrospective study on biopsied jaw lesions in Kuwait, periapical COD comprised 3.3% of the COD cases (Ali, 2011), while a Brazilian study showed an almost equal frequency of periapical COD (11.9%) compared to this study (Netto *et al*., 2013).

Periapical COD exhibits a predilection for middle aged women of African descent and is seldom seen under the age of 20 years (Brannon and Fowler, 2001; Su *et al*., 1997). In this study periapical COD had a mean age of 57.1 years and an age range between 30-87 years. Almost all (15/16; 93.8%) cases of periapical COD in this series presented in females, a finding similar to a Pennsylvanian study that reported (12/13; 92.3%) cases in females (Owosho *et al*., 2013), but differs from a Thai study which observed all four periapical COD cases in males (Worawongvasu and Songkampol, 2010).

Current knowledge observed the presence of two rare forms of COD subtypes, expansive osseous dysplasia (Noffke and Raubenheimer, 2011) and a hereditary / familial form of COD (Sedano *et al*., 1982. Expansive COD was the fourth COD subtype encountered in this series and represented 0.025% of all COD cases diagnosed on biopsy in our population sample. This relatively low prevalence is similar to two other South African studies where expansive COD accounted for less than 1% and 0.35% of all COD cases (Noffke and Raubenheimer, 2011; Raubenheimer *et al*., 2016). The ages of the six patients (4.2%) with expansive COD in the present study ranged between 30.5 and 55 years with a mean age of 42.3 years, which was slightly younger than for florid COD (53.5 years). Raubenheimer *et al,* (2016) reported a mean age of 34.6 years for expansive COD and a predilection for females. In the current study four of the patients with expansile COD were females and two were males. None of these patients reported a positive family history of COD. Two of the six cases involved the maxilla, one involved the mandible and three cases affected both jaws. This contrasts with the occurrence of expansive OD in the study by Noffke and Raubenheimer (2011) and Raubenheimer *et al,* (2016), where the majority of cases were seen in the mandible (Noffke and Raubenheimer, 2011; Raubenheimer *et al*., 2016). Other than reports of expansive COD in South African studies, there is one study from India, which described the case of an aggressive, expansive COD presenting in the maxilla of a 46-year old female patient (Singh *et al*., 2016)

The fifth COD subtype in this study was the familial/hereditary form of COD, which represented 2.8% of the COD subtypes. The proportion of familial COD observed in this study is difficult to

compare with previous reports since most familial COD cases were published as isolated case reports and not studied in relation to the other variants of COD. Further there are only a few studies in the literature dealing with the hereditary pattern of this disease. As pointed out earlier, Sedano *et al*, (1982) described ten cases of familial COD over three generations in the same family under the term of "autosomal dominant cemental dysplasia" (Sedano *et al*., 1982). Young *et al*, (1989) reported 11 cases of familial COD among a Caucasian family over five generations. Also presenting in a Caucasian family, Oikarinen *et al*, (1991) described three cases of COD in a father and his two children. Coleman *et al*. (1996) later reported the same COD disease in a mother and her two children in a South African family. In recent studies Sim *et al*, (2014) observed the first case of familial COD in a mother and her identical twins in a Korean family. Based on a literature survey, the mean age at diagnosis for the familial form of COD is 27.4 years (Sedano *et al*., 1982; Young *et al*., 1989; Oikarinen *et al*.,1991; Coleman *et al*.,1996; Hatori *et al*., 2003; Sim *et al*., 2014; Thorawt *et al*., 2015; Kucukkuet *et al*., 2016). In more than 90% of cases, where site of the lesion was stated, both jaws were affected. The four patients with familial COD in this study had an onset at a younger age with a mean age of 29.7 years. One patient was a male, two were females and the gender was not stated in the fourth case. Both jaws were affected in three of the four patients. Akin to the sporadic form of this disease, familial COD also exhibits a female predilection with an almost 2:1 female to male ratio (Sedano *et al*., 1982; Young *et al.,* 1989; Oikarinen *et al*.,1991; Coleman *et al*.,1996; Hatori *et al.,* 2003; Sim *et al*., 2014; Thorawt *et al*., 2015; Kucukkuet *et al*., 2016). Although the observational extent of familial COD is limited, future studies are needed to establish genetic reasons for this phenomenon.

Osteomyelitis and SBC are well known complications reported in COD. In the current study 73.8% (174/237) of the COD cases were symptomatic at diagnosis and histological examination of the surgically debrided tissue confirmed COD with osteomyelitis. The frequency of chronic suppurative osteomyelitis presenting as a complication of COD varies in different studies. Melrose *et al*. (1976), Kawai *et al*. (1999), Alsufyani and Lam (2011), Owosho *et al*. (2013) and Netto *et al*. (2013) reported infected COD prevalence rates of 5.9%, 14.8%, 11.3%, 5.7% and 4% in their studies on COD. Since the selection of cases in this study was based on histological diagnoses there is an inherent bias that includes cases with pre-existing infection warranting surgical debridement as part of patient management. This may partially explain the discordance in the frequency of COD associated with CSOM between the present study and those of previous studies in the literature. Interestingly, however, those studies that report low prevalence rates of infected COD are from non-African countries, while an African study reported a substantially higher frequency of infected COD, in the order of 78.7%, in their COD study sample (Elbeshir and Alhadad, 2017). Their data included all symptomatic cases of florid COD as well as asymptomatic cases detected during routine radiographic examination at the Khartoum Dental Hospital in Sudan (Elbeshir and Alhadad, 2017). In another African study where, similar to this study, data was derived from a histopathology register in Uganda, the authors reported infected COD in 47% of cases in their COD study population (Muwazi and Kamulegeya, 2015).

The higher percentage of symptomatic cases in studies from Africa may be related to limited preventive and conservative dental services in these countries as well as limited use of routine panoramic radiography in public dental clinics (Elbeshir and Alhadad, 2017). In keeping with the current study findings, most cases of infected COD reported in the literature were of the florid type

(Melrose *et al*., 1976; Alsufyani and Lam, 2011; Owosho *et al*., 2013; Netto *et al*., 2013; Muwazi and Kamulegeya, 2015; Elbeshir and Alhadad, 2017). The extensive nature of the sclerotic masses of florid COD increase the susceptibility of the avascular bone to infection with resultant CSOM. There were 355 cases with a histologically confirmed diagnosis of CSOM without features of COD diagnosed in the department during the period of this study. Together with the 174 cases of infected COD this brings the total number of all cases of CSOM in this study to 529 cases. Hence, 32.9% of all cases of CSOM in this study represented cases of infected COD. This frequency of CSOM presenting as a complication of COD is higher than that reported in other studies, including those studies from Africa. The reason for this finding is not evident from this study. Future studies investigating the source of infection in these COD cases as well as possible co-morbidities in this patient population are required to determine the causative factors for the relatively higher frequency of infected COD found in South Africa. Elbeshir and Alhadad (2017) reported 21.4% of their CSOM cases secondary to COD. In this study males were significant more likely to be diagnosed with CSOM than females. Many studies also report a significant male predominance for non-COD type CSOM (Simpson *et al*., 2001; Yeoh *et al*., 2005). Yet in other studies an equal gender predilection has been reported (Daramola and Algabe, 1982). A slight female preponderance was shown in a West African population where 24 cases of CSOM were seen in males and 36 cases in females out of 60 cases of osteomyelitis secondary to osteoradionecrosis (Khullar *et al*., 2012).

In the current work, both infected COD and CSOM were significantly more common in the mandible than the maxilla or than in both jaws. This is thought to be related to the well-known differences in blood supply and bone density between the mandible and the maxilla (Hudson, 1993; Fullmer *et al*., 2007). In this study CSOM not associated with COD was seen more frequently

than infected COD in the maxilla, however, the difference was not statistically significant. The higher frequency of CSOM not related to COD than infected COD in the maxilla may be related to the smaller sample size of COD in the maxilla (30 cases) compared to CSOM of the maxilla (58 cases). The rate of infected COD in the maxilla nevertheless approached 56.7%, highlighting the effect of bone sclerosis in COD that eventually compromises the normally richly vascular maxillary bone.

The other complication of COD in this study was SBC. There were 11 (11/237; 4.6%) cases of COD associated with SBC, while over the same study period there were 11 cases of SBC without associated COD. The frequency of SBC presenting as a complication of COD found in this study is substantially lower than that reported by Melrose *et al*, (1976) who found 14 (41.4%) out of 34 COD cases associated with SBC. Alsufyani and Lam (2011) described this complication in 12.7% of their cases while SBC was not reported as a complication in any of the 100 COD cases reported by Netto *et al*, (2013). Similarly no SBC were reported in the studies by Owosho *et al*, (2013), Muwazi and Kamulegeya, (2015), Kawai *et al*, (1999), Fun-Chee and Jinn-Fei, (1989), Elbeshir and Alhadad, (2017). All 11 cases were seen in females in this study and in individuals almost two decades older than patients with SBC unassociated with COD. Although our sample size was too small for statistical analysis, periapical COD appeared to present with this complication more often than the other COD subtypes. In the study by Alsufyani and Lam (2011) of the 15 COD cases with SBC, 10 cases (66.7%) were seen in periapical COD (Alsufyani and Lam, 2011), however, in the study by Melrose *et al.* (1976) which comprised exclusively of patients with florid COD, SBC was seen in 41.1% (14/34) of these cases. Further studies comprising larger samples of each COD subtype are required to determine whether a strong association exists between the

COD subtype and the risk of SBC or whether host factors also play a role in the development of this complication. Chadwick *et al,* (2011) reported that out of 91 patients with SBC, 25 % of the patients had co-existing COD, while in this study out of 22 patients with SBC, 50 % were seen in the context of COD. The higher frequency seen in this study is likely because most cases of COD with SBC present with expansile lesions in the jaw causing patients to seek treatment for the swelling which is subsequently biopsied for a definitive diagnosis. This is in contrast to SBC in younger patients which seldom causes jaw expansion and unless panoramic radiography is routinely performed may go unnoticed.

CHAPTER 6

6.1 Conclusions

- Of the 23,288 specimens submitted for histopathological examination over the study period 237 cases of COD were found. This is the largest series of COD cases thus far reported in South Africa.
- The age range of the patients in this series diagnosed with COD was between 9-87 years and the mean age was 53.4 years.
- Florid COD showed a clear trend of increasing with age, peaking in the 51-60 year age group and then decreasing thereafter.
- More than 90% of the cases were seen in females.
- COD mainly affected the mandible (62.4%), followed by involvement of both jaws (24.5%) and the maxilla (13.1%).
- Florid COD predominated (65%) over the other COD subtypes; and was followed by focal COD (16.8%), periapical COD (11.2%), expansive COD (4.2%) and familial COD (2.8%).
- 73.8% of the COD cases were symptomatic at diagnosis and histological examination of the surgically debrided tissue confirmed COD with CSOM.
- This study showed the highest frequency of CSOM presenting as a complication of COD that has thus far been reported in the literature, with 33% of all cases of CSOM in this study being associated with COD.
- There was no significant association between any of the COD subtypes and CSOM ($p > 0.05$).

- Twenty patients re-presented for treatment during the study period. The average period from the initial patient presentation to when they re-presented was 23.2 months.
- An equal number of SBC were seen in patients with and without COD.

6.2 Recommendations arising from this study

Future studies investigating the source of infection in these COD cases as well as possible co-morbidities in this patient population are required to determine the causative factors for the relatively higher frequency of infected COD found in South Africa.

6.3 Limitations of this study

The COD subtypes were documented in the histopathology reports based on the radiographic findings provided with the biopsy sample in only 60% (143/237) of the cases. The COD subtype could not be determined from the histopathology reports in 94 cases.

The relative brevity of clinical information contained in the histopathology reports regarding the potential source of infection in cases of infected COD precluded study of the most prevalent causes of infection in our cases.

In many cases of periapical and florid COD, the distinctive clinico-radiographic patterns may allow a strong presumptive clinical diagnosis and a biopsy is avoided to minimise the risk of onset of symptomatic COD. Hence the exact incidence of COD in the South African population cannot be assessed from this study.

REFERENCES

Abramovitch, K. and Rice, D.D. (2016). Benign Fibro-osseous Lesions of the Jaws. *Dent Clin North Am, 60*(1), 167-193.

Ackermann, G.L. and Altini, M. (1992). The Cementomas A clinicopathological Re-appraisal. *J Dent Assoc S Afr, 47*(5), 187-194.

Aitasalo, K., Niinikoski, J., Grénman, R. and Virolainen, E. (1998). A modified Protocol for Early Treatment of Osteomyelitis and Osteoradionecrosis of the Mandible. *Head Neck, 20*(5), 411-417.

Ali, M.A. (2011). Biopsied Jaw Lesions in Kuwait: A six-year Retrospective Analysis. *Med Princ Pract, 20*(6), 550-555.

Alsufyani, N.A. and Lam, E.W. (2011). Osseous (cemento-osseous) Dysplasia of the Jaws: Clinical and Radiographic Analysis. *J Can Dent Assoc*, 77, b70.

Barnes, L., Eveson, J.W., Reichart, P. and Sidransky, D. (2005). World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours. Lynon: *IARC* Press.

Brannon, R.B. and Fowler, C.B. (2001). Benign Fibro-osseous Lesions: A review of Current Concepts. *Adv Anat Pathol. 8*(3), 126-143.

Butt, F.M.A., Ogengo, J., Bahra, J., Chindia, M.L., Dimba, E.A. and Wagaiyu, E. (2012). A 19-year audit of Benign Jaw Tumours and Tumour-like Lesions in A teaching Hospital in Nairobi, Kenya. *Open J Stomatol*, *2*(01), 54.

Chadwick, J.W., Alsufyani, N.A. and Lam, E.W.N. (2011). Clinical and Radiographic Features of Solitary and Cemento-osseous Dysplasia-associated Simple Bone Cysts. *Dentomaxillofac Radiol*, *40*(4), .230-235.

Cho, B.H., Jung, Y.H. and Nah, K.S. (2007). The Prevalence, Clinical and Radiographic Characteristics of Cemento-osseous Dysplasia in Korea. *Korean J Oral Maxillofac Radiol, 37*(4), 185-189.

Coleman, H., Altini, M., Kieser, J. and Nissenbaum, M. (1996). Familial Florid Cemento-osseous Dysplasia--A case Report and Review of the Literature. *J Dent Assoc S Afr, 51*(12), 766-770.

Daramola, J.O. and Ajagbe, H.A. (1982). Chronic Osteomyelitis of the Mandible in Adults: A clinical Study of 34 Cases. *Br J Oral Surg, 20*(1), 58-62.

Elbeshir, E.I. and Alhadad, M. (2017). Florid Cemento-osseous Dysplasia: Analysis of 47 Sudanese Cases and Review of the Literature. *Oral Surg, 10*(4), 216-221.

El-Naggar A.K., Chan J.K.C., Grandis J.R., Takata T., Slootweg P.J. eds. (2017). *WHO Classification of Head and Neck Tumors.* 4th ed. Lyon, France: *IARC* Press, 251-255.

Eversole, R., Su, L. and ElMofty, S. (2008). Benign Fibro-osseous Lesions of the Craniofacial Complex A review. *Head Neck Pathol, 2*(3), 177-202.

Fullmer, J.M., Scarfe, W.C., Kushner, G.M., Alpert, B. and Farman, A.G. (2007). Cone Beam Computed Tomographic Findings in Refractory Chronic Suppurative Osteomyelitis of the Mandible. *Br J Oral Maxillofac Surg, 45*(5), 364-371.

Fun-chee, L. and Jinn-fei, Y. (1989). Florid Osseous Dysplasia in Orientals. *Oral Surg Oral Med Oral Pathol, 68*(6), 748-753.

Galgano, C., Samson, J., Küffer, R. and Lombardi, T. (2003). Focal Cemento-osseous Dysplasia Involving a mandibular Lateral Incisor. *Int Endod J, 36*(12), 907-911.

Gonçalves, M., Píspico, R., Alves, F.D.A., Lugão, C.E.B. and Gonçalves, A. (2005). Clinical, Radiographic, Biochemical and Histological Findings of Florid Cemento-osseous Dysplasia and Report of A case. *Braz Dent J*, *16*(3), 247-250.

Hatori, M., Ito, I., Tachikawa, T. and Nagumo, M. (2003). Familial Florid Cemento-osseous Dysplasia. *Asian J Oral Maxillofac Surg Med Pathol*, *15*(2), 135-137.

Horner, K. and Forman, G.H. (1988). Atypical Simple Bone Cysts of the Jaws. II: A possible Association with Benign Fibro-osseous (cemental) Lesions of the jaws. *Clin Radiol*, *39*(1), 59-63.

Hudson, J.W. (1993). Osteomyelitis of the Jaws: A 50-year Perspective. *J Oral Maxillofac Surg*, *51*(12), 1294-1301.

Hwang, E.H. and Lee, S.R. (1987). A clinical and Radiographic Study of 104 Cases with Cementoma. *Oral Radiol*, *3*(1), 19-29.

Jerjes, W., Banu, B., Swinson, B. and Hopper, C. (2005). Florid Cemento-osseou Dysplasia in A young Indian Woman. A case report. *Br Dent J*, *198*(8), 477-478.

Kawai, T., Hiranuma, H., Kishino, M., Jikko, A. and Sakuda, M. (1999). Cemento-osseous Dysplasia of the Jaws in 54 Japanese Patients: A radiographic Study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, *87*(1), 107-114.

Khullar, S.M., Tvedt, D., Chapman, K. and Herlofson, B.B. (2012). Sixty Cases of Extreme Osteonecrosis and Osteomyelitis of the Mandible and Maxilla in a West African Population. *Int J Oral Maxillofac Surg*, *41*(8), 978-985.

Kim, S.G. and Jang, H.S. (2001). Treatment of Chronic Osteomyelitis in Korea. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, *92*(4), 394-398.

Kolomvos, N., Theologie-Lygidakis, N., Christopoulos, P. and Iatrou, I. (2013). Benign Fibro-osseous Lesions of the Jaws in Children. A 12-year retrospective study. *J Craniomaxillofac Surg*, *41*(7), 574-580.

Koorbusch, G.F., Fotos, P. and Goll, K.T. (1992). Retrospective Assessment of Osteomyelitis:Etiology, Demographics, Risk factors, and Management in 35 Cases. *Oral Surg Oral Med Oral Pathol*, *74*(2), 149-154.

Kramer, I.R., Pindborg, J.J. and Shear, M. (1992). Histological Typing of Odontogenic Tumours. WHO International Classification of Tumours. *Springer-Verlag. Berlin*.

Kucukkurt, S., Rzayev, S., Baris, E. and Atac, M.S. (2016). Familial Florid Osseous Dysplasia: A report with Review of the Literature. *BM J Case Rep*, *2016*, bcr2015214162.

Lasisi, T.J., Adisa, A.O. and Olusanya, A.A. (2014). Fibro-osseous Lesions of the Jaws in Ibadan, Nigeria. *Oral Health Dent Manag*, 13, 41-44.

MacDonald-Jankowski DS. (2004) Fibro-osseous Lesions of the Face and Jaws. *Clin Radiol*. 11-25.

MacDonald-Jankowski, D.S. (2003). Florid Cemento-osseous Dysplasia: A systematic Review. *Dentomaxillofac Radiol*, *32*(3), 141-149.

MacDonald-Jankowski, D.S. (2008). Focal Cemento-osseous Dysplasia: A systematic Review. *Dentomaxillofac Radiol,* 37(6), 350-360.

Mahomed, F., Altini, M., Meer, S. and Coleman, H. (2005). Cemento-osseous Dysplasia with Associated Simple Bone Cysts. *J Oral Maxillofac Surg*, *63*(10), 1549-1554.

Malik, S. and Singh, G. (2014). Chronic Suppurative Osteomyelitis of the Mandible: A Study of 21 Cases. *J Oral Health Dent Manag*, *13*(4), 971-974.

Mehta RV, Khan S. (2011). Florid Cement-osseous Dysplasia: A case report. *Indian Dent Res Review*. 3, 22–23.

Melrose, R.J., Abrams, A.M. and Mills, B.G. (1976). Florid Osseous Dysplasia: A clinical-Pathologic Study of Thirty-four Cases. *Oral Surg Oral Med Oral Pathol*, *41*(1), 62-82.

Mupparapu, M., Singer, S.R., Milles, M. and Rinaggio, J. (2005). Simultaneous Presentation of Focal Cemento-osseous Dysplasia and Simple Bone Cyst of the Mandible Masquerading as a Multilocular Radiolucency. *Dentomaxillofac Radiol*, *34*(1), 39-43.

Muwazi, L.M. and Kamulegeya, A. (2015). The 5-year Prevalence of Maxillofacial Fibro-Osseous Lesions in Uganda. *Oral Dis*, *21*(1).

Netto, J.D.N.S., Cerri, J.M., Miranda, Á.M.M.A. and Pires, F.R. (2013). Benign Fibro-Osseous Lesions: Clinicopathologic Features From 143 Cases Diagnosed in an Oral Diagnosis Setting. *Oral Surg Oral Med Oral Pathol Oral Radiol*, *115*(5), 56-e65.

Neville, B.W. and Albenesius, R.J. (1986). The Prevalence of Benign Fibro-osseous Lesions of Periodontal Ligament Origin in Black Women: A radiographic Survey. *Oral Surg Oral Med Oral Pathol*, *62*(3), 340-344.

Neville, B.W., Damm, D.D., Chi, A.C. and Allen, C.M. eds. (*2015). Oral Maxillofac Pathol*. 4th ed. *Elsevier Health Sciences*, 596-602.

Noffke, C.E. and Raubenheimer, E.J. (2011). Expansive Osseous Dysplasia: Report of 9 Lesions in An African Population Sample and A review of the Literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, *111*(2), e35-e41.

Ogunsalu, C. and Miles, D. (2005). Cemento-osseous Dysplasia in Jamaica: Review of Six Cases. *West Indian Med J, 54*(4), 264-267.

Ogunsalu, C.O., Lewis, A. and Doonquah, L. (2001). Benign Fibro-osseous Lesions of the Jaw Bones in Jamaica: Analysis of 32 Cases. *Oral Dis*, *7*(3), 155-162.

Oikarinen, K., Altonen, M. and Happonen, R.P. (1991). Gigantiform Cementoma Affecting A caucasian Family. *Br J Oral Maxillofac Surg*, *29*(3), 194-197.

Ongole, R. and Praveen, B.N. eds. (2014). Textbook of Oral Medicine, Oral Diagnosis and Oral Radiology-E-Book. 2nd ed. *Elsevier Health Sciences*, 569-570

Owosho, A.A., Potluri, A. and Bilodeau, E.A. (2013). Osseous Dysplasia (cemento-osseous dysplasia) of the Jaw Bones in Western Pennsylvania Patients: Analysis of 35 Cases. *Pa Dent J*, *80*(6), 25-29.

Pereira, D.L., Pires, F.R., Lopes, M.A., Carlos, R., Wright, J.M., Patel, P., van Heerden, W., Uys, A. and Vargas, P.A. (2016). Clinical, Demographic, and Radiographic Analysis of 82 Patients Affected by Florid Osseous Dysplasia: An international Collaborative Study. *Oral Surg Oral Med Oral Pathol Oral Radiol*, *122*(2), 250-257.

Pindborg, J.J., Kramer, I.R. H. and Torloni, H. (1971). Histological Typing of Odontogenic Tumours, Jaw Cysts, and Allied Lesions. WHO International Histological Classification of Tumours, Geneva: WHO, NO. 5, 31-34.

Raubenheimer, E.J., Noffke, C.E. and Boy, S.C. (2016). Osseous Dysplasia with Gross Jaw Expansion: A review of 18 Lesions. *Head Neck Pathol*, *10*(4), 437-443.

Saito, Y., Hoshina, Y., Nagamine, T., Nakajima, T., Suzuki, M. and Hayashi, T. (1992). Simple Bone Cyst: A clinical and Histopathologic Study of Fifteen Cases. *Oral Surg Oral Med Oral Pathol 74*(4), 487-491.

Sedano, H.O., Kuba, R. and Gorlin, R.J. (1982). Autosomal Dominant Cemental Dysplasia. *Oral Surg Oral Med Oral Pathol 54*(6), 642-646.

Sim, Y.C., Bakhshalian, N., Lee, J.H. and Ahn, K.M. (2014). Familial Florid Cemento-Osseous Dysplasia in Mother and Her Identical Twins: A report with Review of the Literatures. *Oral Surg*, *7*(4), 239-244.

Simpson, A.H.R.W., Deakin, M. and Latham, J.M. (2001). Chronic Osteomyelitis. *J Bone Joint surg Br, 83*(3), 403-407.

Singh, P., Shergil, A., Solomon, M. and Carnelio, S. (2016). Osseous Dysplasia: An aggressive Swelling at An uncommon Site. *J Oral Maxillofac Surg Med Pathol*, *28*(3), 264-266.

Speight, P.M. and Carlos, R. (2006). Maxillofacial Fibro-osseous Lesions. *Curr Diag Pathol*, *12*(1), 1-10.

Stafne, E.C. (1934). Periapical Osteofibrosis with Formation of Cementoma. *J Am Dent Assoc*, *21*(10), 1822-1829.

Su, L., Weathers, D.R. and Waldron, C.A. (1997). Distinguishing Features of Focal Cemento-osseous Dysplasia and Cemento-ossifying Fibromas: II. A clinical and Radiologic Spectrum of 316 Cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, *84*(5), 540-549.

Suei, Y., Taguchi, A. and Tanimoto, K. (2007). Simple Bone Cyst of the Jaws: Evaluation of Treatment Outcome by Review of 132 Cases. *J Oral Maxillofac Surg*, *65*(5), 918-923.

Sule, A.A., Iyogun, C.A. and Adeyemi, T.E. (2017). Pattern of Fibro-osseous Lesions of the Jaws in Kano, *Northern Nigeria. J Dent Oral Health,3:074.*

Summerlin, D.J. and Tomich, C.E. (1994). Focal Cemento-osseous Dysplasia: A Clinicopathologic Study of 221 Cases. *Oral Surg Oral Med Oral Pathol*, *78*(5), 611-620.

Thompson, S.H. and Altini, M. (1989). Gigantiform Cementoma of the Jaws. *Head Neck, 11*(6), 538-544.

Thorawat, A., Kalkur, C., Naikmasur, V.G. and Tarakji, B. (2015). Familial Florid Cemento-osseous Dysplasia–case Report and Review of Literature. *Clin Case Rep*, *3*(12), 1034-1037.

Tonioli, M.B. and Schindler, W.G. (2004). Treatment of A maxillary Molar in A patient Presenting with Florid Cemento-osseous Dysplasia: A case report. *J Endod*, *30*(9), 665-667.

Waldron, C.A. (1985). Fibro-osseous Lesions of the Jaws. *J Oral Maxillofac Surg*, *43*(4), 249-262.

White, S.C. and Pharoah, M.J.eds. (2014). Oral Radiology: Principles and Interpretation. 7th ed. *Elsevier Health Sciences*, 354,408-411.

Worawongvasu, R. and Songkampol, K. (2010). Fibro-osseous Lesions of the Jaws: An analysis of 122 Cases in Thailand. *J Oral Pathol Med*, *39*(9), 703-708.

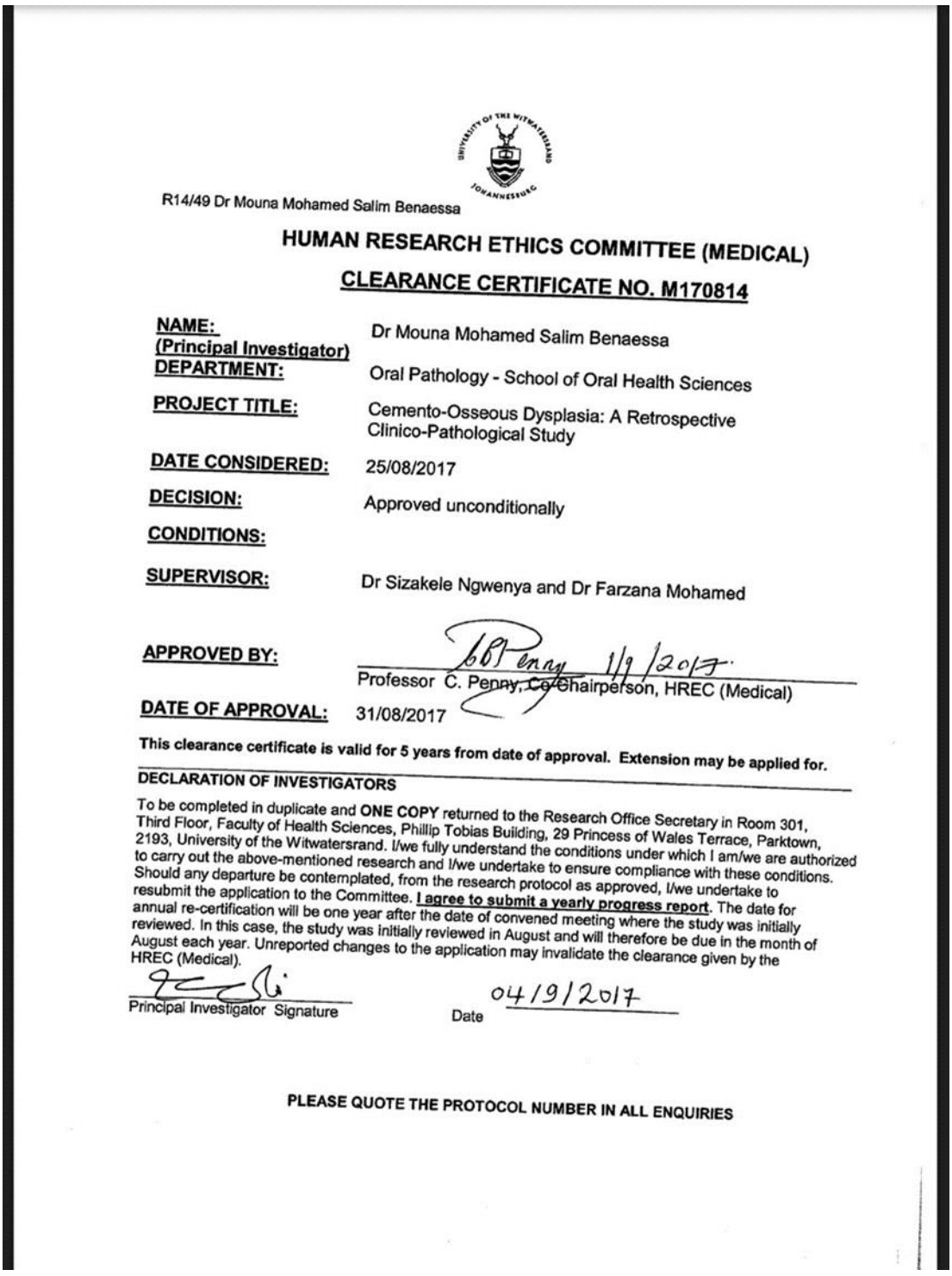
Yahalom, R., Ghantous, Y., Peretz, A. and Abu-Elnaaj, I. (2016). The Possible Role of Dental Implants in the Etiology and Prognosis of Osteomyelitis: A Retrospective Study. *Int J Oral Maxillofac Implants*, *31*(5).

Yeoh, S.C., MacMahon, S. and Schifter, M. (2005). Chronic Suppurative Osteomyelitis of the Mandible: Case Report. *Aust Dent J*, *50*(3), 200-203.

Young, S.K., Markowitz, N.R., Sullivan, S., Seale, T.W. and Hirschi, R. (1989). Familial Gigantiform Cementoma: Classification and Presentation of a large Pedigree. *Oral Surg Oral Med Oral Pathol*, *68*(6), 740-747.

APPENDICES

Appendix A *– Permission from Human Research Ethics Committee*



R14/49 Dr Mouna Mohamed Salim Benaessa

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170814

NAME: (Principal Investigator)	Dr Mouna Mohamed Salim Benaessa
DEPARTMENT:	Oral Pathology - School of Oral Health Sciences
PROJECT TITLE:	Cemento-Osseous Dysplasia: A Retrospective Clinico-Pathological Study
DATE CONSIDERED:	25/08/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Sizakele Ngwenya and Dr Farzana Mohamed
APPROVED BY:	Professor C. Penny, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	31/08/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in August and will therefore be due in the month of August each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 04/9/2017

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix A1*- Permission from Head of Department of Oral Pathology*

Department of Oral Pathology
School of Oral Health Sciences
Faculty of Health Sciences
3E22, 3rd floor, Wits Medical School
7 York Road, PARKTOWN, 2193
Private Bag 3, Wits 2050, South Africa
Tel: 0117172139/97
Fax: 0117172146
Email: HOD: Sizakele.Ngwenya@wits.ac.za
Secretary: Phindile.Mashinini@wits.ac.za

17 July 2017

Human Research Ethics (Medical)
Research Office
Faculty of Health Sciences
University of the Witwatersrand

Dear Sir/Madam

RE: PERMISSION TO CONDUCT A STUDY IN THE DEPARTMENT OF ORAL PATHOLOGY

I, **Dr Sizakele P Ngwenya**, in my capacity **as Head of the Department of Oral Pathology** grant **Dr Mouna Benaessa permission** to access the Department's histopathological reports to retrieve demographic and clinicopathological data as specified in her data collection sheet. This research is in partial fulfilment towards an MDent (Oral Pathology degree, for her study entitled:

Cemento-osseous dyplasia: a retrospective clinico-pathological study

Yours Sincerely,

DR SP NGWENYA
HOD: ORAL PATHOLOGY

Appendix A2 *- Permission from Head of School of Oral Health Sciences*

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

WITS ORAL HEALTH CENTRE

Private Bag X15 Braamfontein, Johannesburg, 2017
Enquiries: Ms Tumelo Marule
Tel: (011)488-4893, Fax 086 406 3196
E-mail: Tumelo.Marule@wits.ac.za

7 August 2017

Dr M Benaessa
MSc Dent Student
Oral Pathology
Faculty of Health Sciences
University of the Witwatersrand
Johannesburg

REGARDING: PERMISSION TO CONDUCT RESEARCH BY COLLECTING DATA FROM THE RECORDS AT THE DEPARTMENT OF ORAL PATHOLOGY.

REFERENCE :HRRC/AUG/04/2017

It is my pleasure to grant final approval to utilize resources at Wits Oral Health Centre in order to conduct your research.
The Hospital Research and Risk Committee allocated a unique reference number to this application – Kindly quote this reference number in all future correspondence regarding this research.

Please note that the Hospital Research and Risk Committee should be informed of the estimated date the research will commence, as well as regular status reports until the research has been concluded. Within a month after conclusion of the research project, a written report must be submitted to the Head of School/CEO, summarizing the final result/outcome as well as the recommendations made based on the research concluded.

Regards,

(Acting HOS)

Prof MS Nemutandani
CEO/Head of School

Appendix A3 *– Title Approval*

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

21 September 2017
Person No: 1454372
PAG

Miss MMS Benaessa
106 Juliana Court
4 Princess Place
Parktown
2193
South Africa

Dear Miss Benaessa

Master of Science in Dentistry: Approval of Title

We have pleasure in advising that your proposal entitled *Cemento-osseous dysplasia: A retrospective clinico-pathological study* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix B *– Raw data*

CASE NO	Age	Gender	Site	COD subtype
1	34	F	Both	Florid COD
2	47	F	NS	NS
3	46	M	Mandible	NS
4	49	F	Mandible	Florid COD
5	46	F	Mandible	NS
6	42	F	Mandible	Periapical COD
7	30	F	Both	Florid COD
8	52	F	Mandible	NS
9	56	F	Mandible	Periapical COD
10	63	F	Mandible	Florid COD
11	61	F	Mandible	Florid COD
12	78	F	Maxilla	NS
13	38	F	Mandible	Focal COD
14	27	M	Maxilla	NS
15	29	M	Mandible	NS
16	58	F	Mandible	NS
17	51	F	Mandible	Florid COD
18	61	F	Mandible	Periapical COD
19	37	F	Maxilla	NS
20	80	F	Mandible	Periapical COD
21	NS	F	Maxilla	NS
22	25	F	Maxilla	NS
23	52	F	Mandible	Florid COD
24	82	F	Mandible	NS
25	36	F	Mandible	Focal COD
26	45	F	Mandible	NS
27	NS	F	Mandible	Focal COD
28	52	F	Maxilla	NS
29	38	F	Mandible	Florid COD
30	60	F	Mandible	Florid COD
31	53	F	Mandible	NS
32	62	F	Both	Florid COD
33	38	F	Maxilla	NS
34	85	F	Mandible	NS
35	56	F	Both	Florid COD
36	56	F	Mandible	NS
37	56	F	Mandible	Focal COD
38	60	F	Mandible	Florid COD
39	43	F	Mandible	NS
40	25	F	Mandible	Florid COD
41	41	F	Mandible	NS
42	34	F	Mandible	Focal COD
43	NS	F	NS	NS
44	57	F	Both	Florid COD
45	67	F	NS	NS
46	61	F	Both	Florid COD
47	58	F	Mandible	NS
48	58	F	Maxilla	NS
49	58	F	Mandible	NS

50	52	F	Both	Florid COD
51	52	F	Mandible	Florid COD
52	67	F	NS	NS
53	56	M	Mandible	Focal COD
54	62	F	Mandible	Florid COD
55	54	F	Mandible	NS
56	39	F	Both	Florid COD
57	NS	F	Both	Florid COD
58	41	F	Mandible	NS
59	70	F	Mandible	NS
60	24	F	Mandible	NS
61	43	F	Mandible	Florid COD
62	57	F	Mandible	NS
63	65	F	Maxilla	NS
64	68	F	Mandible	Focal COD
65	38	F	Both	Florid COD
66	46	F	Both	Florid COD
67	NS	NS	Both	Familial COD
68	60	F	Mandible	Focal COD
69	45	F	Both	Florid COD
70	48	M	Maxilla	NS
71	61	F	Mandible	NS
72	51	F	Both	Florid COD
73	45	F	Maxilla	NS
74	48	F	Both	Florid COD
75	73	F	Both	Florid COD
76	54	F	Mandible	Focal COD
77	60	F	Mandible	NS
78	55	F	Mandible	NS
79	49	F	Mandible	Florid COD
80	52	F	Mandible	NS
81	71	F	Mandible	NS
82	43	F	Mandible	NS
83	58	F	Mandible	NS
84	75	F	Mandible	NS
85	46	F	Mandible	Florid COD
86	48	F	Both	Florid COD
87	49	F	Mandible	NS
88	29	F	Maxilla	NS
89	62	F	Mandible	Focal COD
90	50	F	Mandible	Florid COD
91	41	F	Mandible	Florid COD
92	69	F	Mandible	NS
93	45	F	Both	Florid COD
94	37	M	Mandible	NS
95	59	M	Both	Florid COD
96	65	F	Both	Florid COD
97	45	F	Mandible	Focal COD
98	78	F	Mandible	NS
99	64	F	Mandible	Periapical COD
100	47	F	Maxilla	NS
101	32	F	Both	Expansive Osseous Dysplasia
102	52	F	Mandible	Florid COD

103	41	F	Mandible	Periapical COD
104	41	F	Mandible	Florid COD
105	72	F	Mandible	NS
106	70	F	Both	Florid COD
107	63	F	Mandible	NS
108	56	F	Both	Florid COD
109	43	F	Mandible	NS
110	66	F	Both	Florid COD
111	50	F	Both	Familial COD
112	49	F	Mandible	NS
113	58	F	Both	Florid COD
114	68	F	Mandible	Florid COD
115	31	M	Mandible	Florid COD
116	72	F	Mandible	Florid COD
117	24	F	Mandible	Florid COD
118	62	F	Mandible	Focal COD
119	43	F	Mandible	Florid COD
120	45	F	Mandible	NS
121	54	F	Both	Florid COD
122	30	M	Both	Florid COD
123	70	F	Mandible	NS
124	67	M	Mandible	Focal COD
125	43	F	Mandible	NS
126	41	F	Maxilla	NS
127	36	F	Mandible	Florid COD
128	52	F	Both	Florid COD
129	55	F	Mandible	Florid COD
130	51	F	Mandible	NS
131	54	F	Mandible	NS
132	59	F	Mandible	Florid COD
133	31	F	Mandible	Focal COD
134	23	F	Maxilla	NS
135	45	F	Mandible	Periapical COD
136	67	F	Mandible	Florid COD
137	52	F	Both	Florid COD
138	50	F	Mandible	Florid COD
139	51	F	Maxilla	Focal COD
140	60	F	Mandible	NS
141	66	F	Mandible	NS
142	46	F	Both	Florid COD
143	48	F	Mandible	NS
144	70	F	Mandible	NS
145	35	F	Mandible	NS
146	51	F	Mandible	Florid COD
147	50	F	Mandible	Focal COD
148	30	M	Maxilla	Expansive Osseous Dysplasia
149	68	F	NS	NS
150	25	M	Maxilla	NS
151	58	F	NS	NS
152	54	F	Mandible	NS
153	60	F	Mandible	Focal COD
154	50	F	Maxilla	NS
155	11	M	Both	Familial COD

156	50	F	Mandible	Periapical COD
157	67	F	Mandible	Periapical COD
158	48	F	Mandible	NS
159	44	F	Both	Florid COD
160	56	F	Maxilla	NS
161	43	F	Mandible	NS
162	63	F	Both	Florid COD
163	54	F	Mandible	Florid COD
164	40	F	Mandible	Periapical COD
165	54	M	Maxilla	Focal COD
166	72	F	NS	NS
167	61	F	Mandible	NS
168	62	F	Both	Florid COD
169	85	F	Mandible	Florid COD
170	60	F	Both	Florid COD
171	68	F	Mandible	Florid COD
172	64	F	Mandible	NS
173	63	F	Maxilla	Focal COD
174	80	F	Maxilla	NS
175	66	F	Maxilla	Florid COD
176	46	F	Mandible	NS
177	53	F	Both	Florid COD
178	52	F	Mandible	Florid COD
179	9	F	Maxilla	Florid COD
180	47	F	Both	Florid COD
181	62	F	Mandible	NS
182	34	F	Both	Focal COD
183	64	F	Mandible	NS
184	53	F	Mandible	Florid COD
185	55	F	Mandible	Florid COD
186	74	F	Mandible	NS
187	53	F	Maxilla	NS
188	74	F	Mandible	NS
189	59	F	Both	Florid COD
190	74	F	Mandible	NS
191	87	F	Mandible	Periapical COD
192	66	F	Mandible	NS
193	50	F	Maxilla	NS
194	34	F	Mandible	Florid COD
195	69	F	Mandible	Periapical COD
196	70	M	Mandible	Periapical COD
197	71	F	Mandible	Florid COD
198	78	F	Mandible	Focal COD
199	72	F	Mandible	Periapical COD
200	77	F	Mandible	NS
201	56	F	Mandible	Florid COD
202	54	F	Mandible	NS
203	56	F	Both	Florid COD
204	73	F	Mandible	NS
205	74	F	Both	Florid COD
206	62	F	Both	Florid COD
207	39	F	Both	Expansive Osseous Dysplasia
208	54	F	Both	Florid COD

209	58	F	NS	NS
210	50	F	Both	Florid COD
211	46	F	Mandible	NS
212	47	F	Both	Florid COD
213	83	F	Both	Florid COD
214	46	M	Mandible	Expansive Osseous Dysplasia
215	30	F	Mandible	Periapical COD
216	77	F	Mandible	Florid COD
217	28	F	Maxilla	Focal COD
218	57	F	Mandible	NS
219	61	F	Mandible	NS
220	53	F	Both	Florid COD
221	29	F	Mandible	Familial COD
222	45	F	Mandible	Focal COD
223	50	F	Both	Florid COD
224	53	F	Mandible	Florid COD
225	44	F	Both	Florid COD
226	70	F	Both	Florid COD
227	39	F	Mandible	Periapical COD
228	80	F	Both	Florid COD
229	41	F	Mandible	NS
230	50	F	Both	Florid COD
231	50	F	Both	Florid COD
232	52	F	Both	Expansive Osseous Dysplasia
233	56	F	Maxilla	NS
234	64	F	Mandible	Florid COD
235	45	F	Mandible	Focal COD
236	55	F	Maxilla	Expansive Osseous Dysplasia
237	61	F	Both	Florid COD

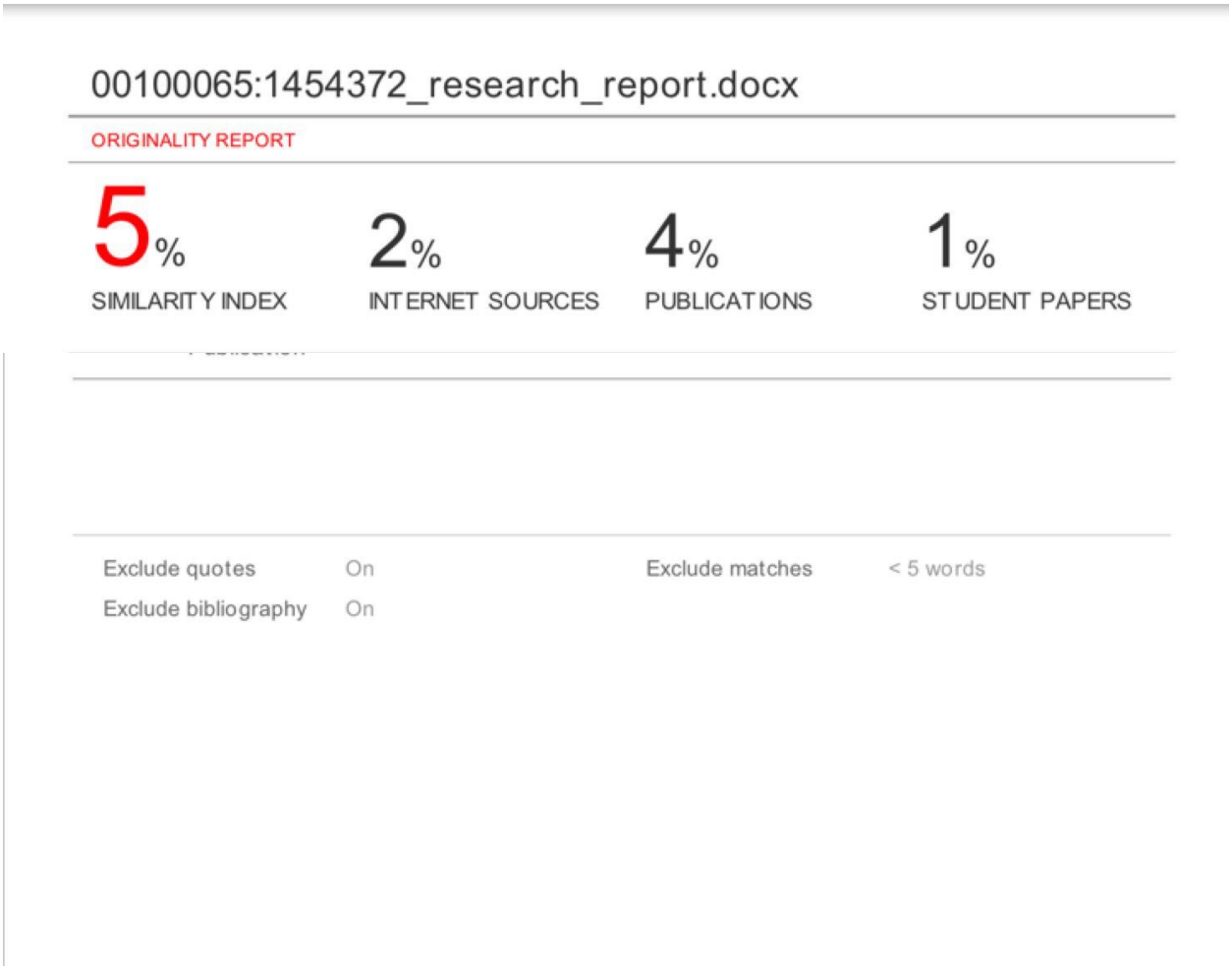
Key to the age groups

Age Group	
<10 years	1
11-20 years	2
21-30 years	3
31-40 years	4
41-50 years	5
51-60 years	6
61-70	7
71-80	8
>80	9

Appendix C *– Re-reported patients during study period*

Age (years)	**Gender**	**Site of COD**	**Types of COD**	**Follow up period**	**No of surgical specimens submitted**	**complications**
42	F	Mandible	Periapical COD	NS	2	SBC
62	F	Both	Florid COD	14 months	2	Infected
50	F	Both	Familial COD	120 months	8	ABC
32	F	Both	Expansive osseous dysplasia	6 months	2	Non-infected
72	F	Mandible	Florid COD	1 months	2	Infected
24	F	Mandible	Florid COD	101 months	3	Infected
67	M	Mandible	Focal COD	6 months	2	Non-infected
41	F	Maxilla	NS	17 months	2	Non-infected
66	F	Mandible	NS	1 month	2	Infected
30	M	Maxilla	Expansive osseous dysplasia	4 months	3	Infected
44	F	Both	Florid COD	45 months	3	SBC
54	M	Maxilla	Focal COD	51 months	2	Infected
66	F	Maxilla	Florid COD	3 months	3	Infected
80	F	Maxilla	NS	2 months	2	Infected
46	F	Mandible	NS	1 months	2	Infected
50	F	Mandible	Periapical COD	47 months	2	Infected
50	M	Maxilla	NS	2 months	2	Infected
50	F	Mandible	Florid COD	19 months	2	Infected
43	F	Mandible	NS	4 months	2	Infected
29	F	Mandible	Familial COD	3 months	2	Infected
NS	F	NS	NS	19 months	2	Infected
49	F	Mandible	Florid COD	NS	2	Infected
56	F	Both	Florid COD	NS	2	Infected
56	M	Mandible	Focal COD	NS	2	Infected
58	F	Mandible	NS	NS	2	Infected
61	F	Mandible	NS	NS	2	Infected
62	F	Both	Florid COD	NS	2	Infected

Appendix D *- Plagiarism Report*



00100065:1454372_research_report.docx

ORIGINALITY REPORT

5%	2%	4%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

Exclude quotes	On	Exclude matches	< 5 words
Exclude bibliography	On		