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RESEARCH ARTICLE

PREVALENCE OF FUNGAL OSTEOMYELITIS OF THE JAWS ASSOCIATED WITH DIABETES MELLITUS IN NORTH KARNATAKA POPULATION: A RETROSPECTIVE STUDY

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ABSTRACT

Although numerous studies have been done worldwide, there is limited data available on demographic profile of fungal osteomyelitis in the North Karnataka population. This study was designed to evaluate the prevalence of fungal osteomyelitis of the jaws associated with diabetes mellitus in North Karnataka population over a period of 10 years. Histologically diagnosed cases of osteomyelitis of the jaws were reviewed from January 2005 to December 2015 and subjected to statistical analysis by Chi-square test for age, gender, site, area and diabetic status. 52% cases were that of fungal osteomyelitis whereas, 48% belonged to non- fungal osteomyelitis. Fungal osteomyelitis was frequently found above 40 years of age (80.76%), more commonly in males (69.23%) and affecting the maxilla (80.76%). It was also noted that fungal osteomyelitis of the jaws was more commonly associated with diabetes mellitus (61.53%).

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INTRODUCTION

Diabetes mellitus is a group of diverse metabolic disorders characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. The word "Diabetes" means to "run through" or "siphon" in Greek denoting the excessive urination associated with the disease and the condition has been recognized since the time of the ancient Egyptians. Greek word "Mellitus" which means "like honey" was added later to reflect the sweet smell and taste of patient's urine. Diabetes mellitus is a growing public health concern worldwide.

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World Health Organization has declared Diabetes Mellitus to be a pandemic. The largest number of diabetics is seen in India which is roughly about 62 million Indians which is more than 7.1% of total adult population. It has been noted that there has been the sharpest rise in the incidence of diabetes in Southern India (11.6%) compared to the other areas in India (Mohan *et al*., 2006). The effect of Diabetes Mellitus includes long term damage, dysfunction and failure of various organs. Complications that are specific to diabetes include retinopathy, nephropathy and neuropathy. The major oral complications of diabetes include periodontal pathologies, salivary and taste dysfunction, neuro sensory oral disorders, infections like bacterial, fungal infections leading to serious complications like rhino cerebral mucormycosis, synergistic necrotizing cellulitis etc. Osteomyelitis of the jaws is one such serious complication of Diabetes Mellitus.

It is an inflammatory condition of the bone, beginning in the medullary cavity and Haversian systems and extending to involve the periosteum of the affected area. Osteomyelitis can also develop due to a fungal infection as a result of the fungus settling in the bone marrow. Fungal infections arise as opportunistic infections at sites which are more conducive to the fungal growth. Oral cavity is one such platform for fungal growth. Fungal Osteomyelitis is almost always a complication of some other offending circumstance like, Diabetes Mellitus that renders host susceptible. Due to altered immunity the fungal organisms can invade the bone resulting in fungal osteomyelitis and eventually bring about the necrosis of bone. Even if bacterial osteomyelitis occurs much more frequently, fungal osteomyelitis is more invasive and can cause serious diagnostic difficulties.

AIMS OF THE STUDY

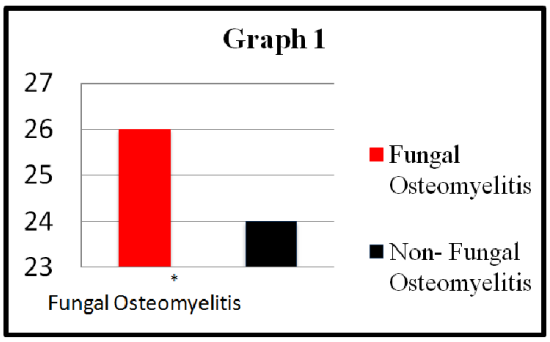
- To evaluate the prevalence of Fungal Osteomyelitis of the jaws in diabetic and non-diabetic individuals in North Karnataka population.
- To assess the clinicopathologic correlation with osteomyelitis of the jaws.
- To understand the pathogenesis and relation between fungal osteomyelitis and diabetes mellitus.
- To create awareness concerning diabetes mellitus and the immense devastation it can lead to.

MATERIALS AND METHODS

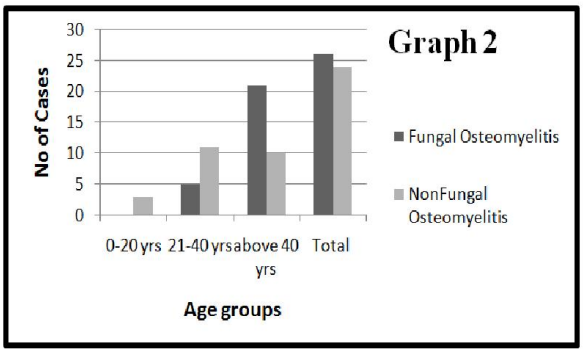
A retrospective study designed over a span of 10 years from January 2005 to December 2015 was carried out. The data was collected from histologically diagnosed cases of Osteomyelitis of jaws from the annals of Department of Oral Pathology and Microbiology, SDM College of Dental Sciences and Hospital, Dharwad in North Karnataka, India. The archival data was evaluated for age, gender, area of involvement, presence or absence of Diabetes Mellitus.

RESULTS

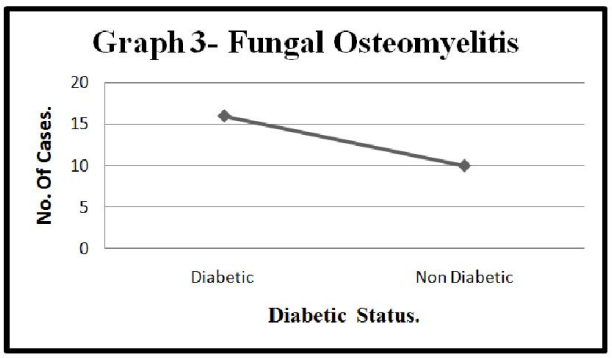
Out of 5503 biopsies received during 10 year period from January 2005 to December 2015, a total of 50 cases were diagnosed as Osteomyelitis of the Jaws excluding that of Soft tissues of the head and neck region. Out of these, 26 cases (52%) were those of fungal osteomyelitis of the jaws. The Non- Fungal osteomyelitis includes Acute Suppurative Osteomyelitis, Chronic Osteomyelitis, Garre's Osteomyelitis, and Non-Specific Osteomyelitis. Graph1 shows the frequency distribution of Fungal and Non- Fungal Osteomyelitis. Graph 2 shows the frequency distribution of all the cases according to the age groups defined. The cases of fungal osteomyelitis ranged from second to eighth decade of life and that of Non-Fungal Osteomyelitis belonged in a wide range from First to seventh decade. The peak incidence of Fungal Osteomyelitis was seen in the age range above 40 years. Among the 26 cases of fungal osteomyelitis, 16 patients (62%) were suffering from Diabetes Mellitus. The records of the remaining 10 patients showed no report of diabetes. Among the Non- Fungal Osteomyelitis only 3 patients had history of Diabetes mellitus.



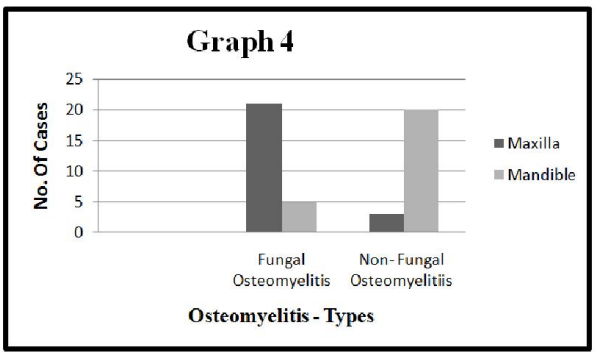
Graph 1. Bar chart showing the distribution of cases of fungal and non-fungal osteomyelitis. * (More than 50%)



Graph 1. Bar chart showing the distribution of cases of fungal and Non-Fungal Osteomyelitis. *(More than 50%)



Graph 3. Line Diagram showing the association between Diabetes Mellitus and Fungal Osteomyelitis



Graph 4. Bar chart showing the distribution of Fungal and Non-fungal Osteomyelitis in Maxilla and Mandible

Out of the total cases of fungal osteomyelitis 21 (81%) were seen to be involving the maxilla whereas only 5 cases (19%) were seen in the mandible. Non- Fungal Osteomyelitis was more common in mandible (21 cases) than in maxilla (3 cases). It was also seen that fungal osteomyelitis affected the anterior maxilla more commonly than posterior, whereas osteomyelitis other than fungal type affected the posterior mandible than the other sites. Statistical Analysis performed using chi-square test in relation to the clinicopathologic parameters including Age, Gender, Area, Site and Diabetic Status in both fungal osteomyelitis and non-fungal osteomyelitis was done. Significant results were obtained with respect to site, area, diabetic status and age. The same are shown below in the table 2.

Table 1. "Warning Signs" Of Diabetes Mellitus.

Signs of Diabetes : General	Signs of diabetes: Oral Cavity
Polyuria	Multiple Periodontal Abscesses
Polydipsia	Xerostomia
Polyphagia	Tingling in tongue
Weight loss	Burning tongue
Fatigue	Pale mucosa
Tingling in feet, heels	Unpleasant taste

Table 2. Clinicopathologic parameters in fungal and non- fungal osteomyelitis with diabetes status

Characteristic		Fungal Osteomyelitis	Non- Fungal Osteomyelitis	p-Value
Age	0-20 years	0	3	0.011*
	20-40 years	5	11	
	>40 years	21	10	
Gender	Male	18	12	NS
	Female	8	12	
Site	Maxilla	21	4	0.000*
	Mandible	5	21	
Area	Anterior	12	4	0.026*
	Posterior	14	20	
Diabetes	Diabetic	16	3	0.000*
	Non Diabetic	10	21	

DISCUSSION

Osteomyelitis is an inflammatory process accompanied by bone destruction and caused by an infecting micro-organism (Lew *et al*., 2004). It is defined as an inflammatory condition of the bone that commences as an infection of the medullary cavity, rapidly involving the Haversian systems and eventually involving the periosteum of the infected areas. It is stated that osteomyelitis of craniofacial skeleton is more difficult to treat than osteomyelitis of other bones; because of the complex craniofacial skeleton anatomy and associated esthetic concerns (Pincus *et al*., 2009). The various types of osteomyelitis include osteomyelitis secondary to contiguous focus of infection, that secondary to vascular insufficiency or that of hematogenous origin (Lew *et al*., 2004). Fungal osteomyelitis of the jaw bones is a type of osteomyelitis arising mainly due to vascular insufficiency created by the effect of the fungus on the endothelial lining of the vessels. Fungal organisms causing osteomyelitis in the craniofacial region include Candida, Zygomycetes and Aspergillus. It is found that aspergillus is the most common organism causing fungal infection followed by Zygomycetes. But infection by Zygomycetes more commonly affects the diabetics than aspergillus. Fungal osteomyelitis of the jaws is more likely to be invasive as compared to bacterial if not diagnosed early and treated. According to experimental studies, an association between Diabetes mellitus and variations in oral mucosa has been observed. These include alterations in healing process of lesions and also the triggering of infectious processes in mucosal lining (Caldeira *et al*., 2004). This correlation is in alliance with the occurrence of Fungal Osteomyelitis in diabetics and the molecular changes in the oral mucosa can be taken as a major tool to foretell such serious infectious culmination. There is ample literature supporting the prevalence of osteomyelitis but there is a paucity of studies done on fungal osteomyelitis and the correlation with Diabetes Mellitus.

In the present study, we found that out of the 50 cases of osteomyelitis, 26 cases were that of fungal osteomyelitis of the jaws. However, in another study (Peravali *et al*., 2012) only 5 cases were diagnosed as fungal osteomyelitis out of 31 cases of osteomyelitis over a period of 5 years from 2002 to 2008.The incidence of fungal osteomyelitis has increased over the years, mainly due to the increased number of patients who are at a risk for this serious fungal infection. These risk factors include the debilitated state of a patient, immunocompromised host defenses as is in case of Diabetes Mellitus, AIDS, and immunosuppression therapy. It may also be due to a decrease in number of cases of bacterial osteomyelitis due to the success of antibiotic therapy or due to increased use of antineoplastic and immunosuppressive agents, broad spectrum antibiotics which suppress the normal bacterial flora, in turn, causing the survival of fungal organisms. In the current study, the peak incidence of fungal osteomyelitis was seen in the age group above 40 years. According to a study done by Rajgopalan S, (Rajgopalan, 2005) fungal osteomyelitis and especially mucormycosis showed a tendency to occur in patients above 45 years. A possible hypothesis for this is that age related changes are seen in adaptive immune system and include, diminished and/or altered cytokine patterns, reduction in clonal expansion and function of antigen specific T and B cells and a decline in antigen presenting cell function. Hence the defense against the fungal invasion is weakened (Renshaw *et al*., 2002).

Another important finding in our study was that out of the 26 cases of fungal osteomyelitis, 16 patients were recorded to be suffering from Diabetes Mellitus whereas in case of osteomyelitis of the other types, only 3 cases were associated with diabetes mellitus. Almost 62% of the patients with fungal osteomyelitis had diabetes. Such a correlation between diabetes and fungal osteomyelitis was also noted in a previous study, where all the 6 cases of fungal osteomyelitis out of 31 cases of osteomyelitis had an association with diabetes mellitus (Peravali *et al*., 2012). It has been noted in literature that diabetes mellitus is the most common (60-81%) predisposing factor for mucormycosis (a form of fungal osteomyelitis) (Bhansali *et al*., 2004). The pathogenesis for the occurrence of fungal osteomyelitis in diabetic individuals can be explained as follows.

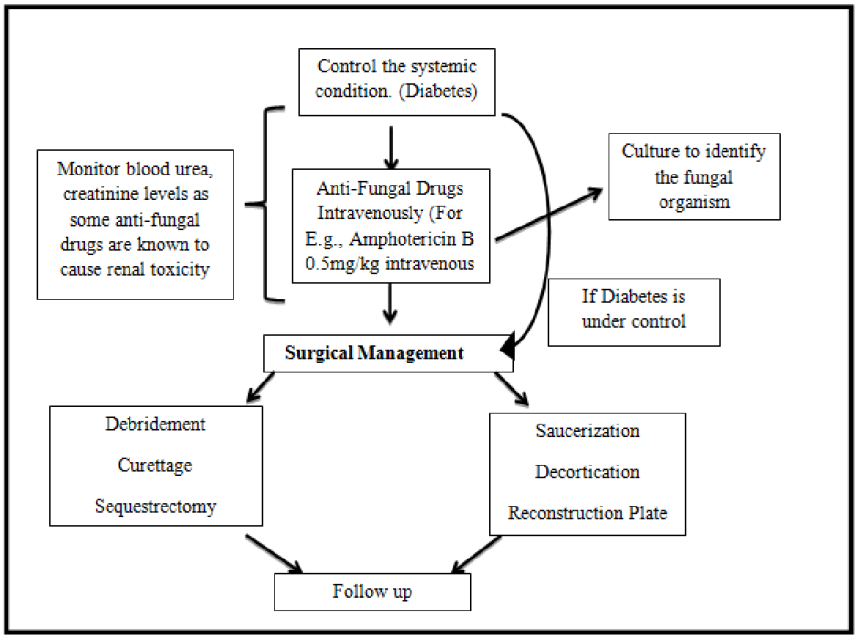
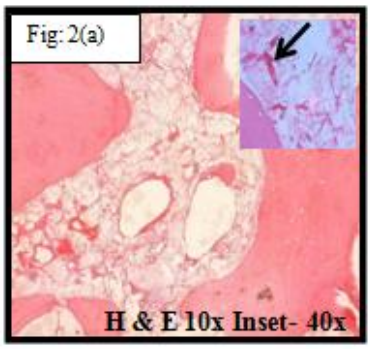
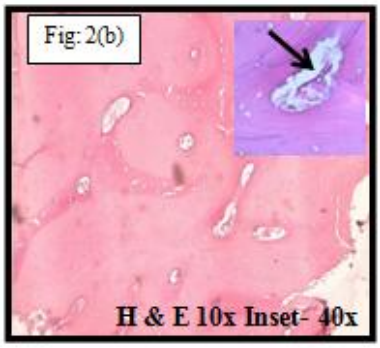


Chart 1. Basic principles in management of fungal osteomyelitis

Figures 1(a) & 1(b). Clinical photographs of fungal osteomyelitis affecting the maxilla. Note the exposed necrosed bone





Figures 2(a) & 2(b). Photomicrographs of Haematoxylin & Eosin stained sections of decalcified bone with numerous fungal hyphae surrounded by non-vital bone. Note the characteristic 'Y' shaped branching and right angled branching (arrows).

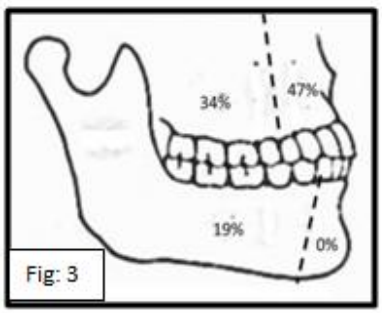


Figure 3. Site distribution of cases of fungal osteomyelitis in maxilla and mandible

In diabetics, phagocytes are dysfunctional and have impaired chemotaxis and defective intracellular killing by both oxidative and non-oxidative mechanisms. In addition, there is presence of hyperglycemia and low pH which is found in patients with diabetic ketoacidosis (DKA). Hence the defense mechanism is debilitated against these fungal organisms. It is also noted that there is markedly enhanced availability of iron in tissues or serum which promotes aggressive invasive growth of acquired fungal spores. The excessive glycosylation of proteins such as transferrin and ferritin, owing to poorly controlled diabetes, results in decreased affinity of these proteins to bind iron, making that important element available for Mucorales. Similarly, lower blood pH due to ketoacidosis and other forms of acidosis compromises the affinity of transferrin to bind iron. Also elevated glucose and iron levels upregulate GRP78 expression and promote endothelial cell invasion and damage by Rhizopus Oryzae in a receptor dependent manner. Therefore, interaction of fungal cells with endothelium lining of blood vessels represents a critical step in progression of disease (Ibrahim *et al*., 2012; Ibrahim *et al*., 2013).

It was seen in the current study that the incidence of fungal osteomyelitis of maxilla was more than in the mandible. Out of 26 cases, 21 cases (81%) were seen in the maxilla and only 5 cases (19%) were seen in the mandible.

However, Non- Fungal osteomyelitis was more common in mandible (20 cases) than in maxilla (4 cases). Maxilla rarely undergoes necrosis due to its rich vascularity. But in case of fungal osteomyelitis, this fungal infection usually originates from paranasal sinuses. The fungus invades the blood vessels and subsequently spreads through them. Fungal hyphae form thrombi within blood vessels that reduce vascularity to the tissues which ultimately causes necrosis. Peripheral Vascular disease due to microangiopathy and atherosclerosis in diabetic patients also causes local tissue ischemia and increased susceptibility to infections (Auluck., 2007). Auluck A in a study done in 2007 noted that thrombosis of the internal maxillary artery caused by mucormycotic infection as well as chronic diabetes in the patient had resulted in necrosis of the maxilla (Auluck., 2007). In case of Non- Fungal osteomyelitis, it is said to be relatively uncommon in maxilla compared to mandible due to porous nature of bone, significant collateral blood flow and thin cortices.

Table 1 illustrates the "warning signs" of diabetes mellitus including the general signs and also the signs seen in the oral cavity. It is imperative for a clinician to know these signs and also to understand the importance of these in the management of patients with diabetes. The management of fungal osteomyelitis of jaws in diabetic patients is unlike that in a non-diabetic. Fungal osteomyelitis is a fulminating and highly invasive disease, hence should be treated thoroughly. The management of fungal osteomyelitis includes the steps shown in the chart 1. Surgical management becomes necessary as the necrosed bone has to be removed. If not, the anti-fungal drugs will not be efficient. After the surgical treatment the prosthetic rehabilitation of the patient is obligatory. Another important aspect is the follow up for any signs of remnant of the fungal infection, as it is known to recur if the pathogenic fungal organism is not removed completely.

If Fungal Osteomyelitis of the jaws is not treated promptly, the infection can spread through ethmoidal artery via the sphenopalatine artery to the apex of the orbit and cavernous sinus. This eventually can result in cerebral ischemia and death (Mohanty *et al*., 2012). Moreover most of the patients did not agree for culture tests which should have been done to confirm the type of fungal organism involved. As mentioned earlier the most common organism causing fungal infections is aspergillus (69.7%) followed by candida (22.2%) and Zygomycetes (Mucorales) (8.1%) (George *et al*., 2004). The world's highest number of cases of invasive zygomycosis is reported in India (Chakrabarti *et al*., 2008). It is also found that the majority of cases of fungal infection are found in patients with Diabetes and this was also confirmed in the present study. The clinical diagnosis of these fungal infections is challenging as most of the clinical symptoms are not specific and early clinical features mimic that of sepsis. Moreover the cultures may become positive only in the later stages of the disease. Hence, the mortality is high in case of fungal osteomyelitis and invasive rhino-cerebral mucormycosis.

Diabetes mellitus is believed to be a silent killer. It can lead to a group of diverse complications along with serious manifestations like fungal osteomyelitis of the jaw bones. A dental practitioner should be aware of these complications and understand the devastation it can lead to. Awareness regarding the measures to be taken in treating and managing these diabetics in a dental clinic should be created. It is sometimes possible that a dental practitioner is the first to make a patient aware of his/her diabetic status based on the oral signs and symptoms. As mentioned earlier in the table 1 some "warning signs" of diabetes are also seen in the oral cavity and these can be helpful in cautioning the patient before the more serious complications develop. Moreover if the patient undergoes routine blood tests and regular checkups, diabetes can be controlled and the complications can be avoided. Hence measures should be taken to control diabetes and make patients aware of the consequences of poorly controlled diabetes.

Conclusion

The study revealed that there is a major correlation between fungal osteomyelitis and Diabetes. Almost 62% of fungal osteomyelitis cases had Diabetes Mellitus. There has been an increase in the incidence of fungal osteomyelitis in the past decade. The maxilla (81%) was seen to be involved more commonly than mandible (19%). The gravity of this serious manifestation of diabetes should be well understood and a platform should be created for significant measures whether it is by a general or a dental practitioner. Besides, there is an urgent requisite for good diagnostic mycology laboratories, early diagnosis, management and improvement of the anti-fungal approaches in India. However, there is a dearth of studies done in diabetic individuals and fungal osteomyelitis hence further studies should be taken up to enlighten the community about such fatal consequences of Diabetes.

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