ISSN 2706-6819 Vol.5, Issue 10: 127-131, DOI: 10.25236/IJFM.2023.051020

The correlation between the main pathogenic bacteria and bone metabolism markers in mandibular osteomyelitis

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Abstract: *Investigating the relationship between pathogenic bacteria and bone metabolism indicators in patients with osteomyelitis of the jaw, in order to aid in understanding the mechanisms of the disease and improving treatment strategies. We retrospectively analyzed the basic information and laboratory test results of 34 patients diagnosed with osteomyelitis of the jaw who were treated at the Department of Oral and Maxillofacial Surgery of the First Affiliated Hospital of Xinjiang Medical University from December 1, 2022 to May 1, 2023. Data was analyzed using SPSS27.0 software. Among the 34 patients, 6 were under 40 years old, 16 were 60 or older, and 12 were between 40 and 60 years old. There were 15 male and 19 female patients. The types of osteomyelitis of the jaw were pyogenic (50%), radiation-induced (23.5%), and drug-induced (26.5%). There were no statistically significant differences in age or gender between different types of osteomyelitis of the jaw and bone metabolism indicators. Additionally, there were no significant differences in oral normal flora and non-oral normal flora on bone metabolism indicators, as well as bacterial culture results. However, older age was associated with higher parathyroid hormone levels, which may play a role in inhibiting normal bone metabolism.*

Keywords: *osteomyelitis of the jaw; bacteria; bone metabolism*

1. Introduction

Mandibular osteomyelitis is an inflammatory condition caused by bacterial infection, as well as physical or chemical factors, leading to pathological changes in the periosteum, cortical bone, bone marrow, as well as blood vessels and nerves within the medullary cavity. According to statistics, the global incidence of mandibular osteomyelitis is approximately 3-4 per 100,000 population [1]. Based its etiology, it can be classified into infectious and non-infectious osteomyelitis, with the majority of cases being caused by bacterial infections [2,3,4]. Previous studies have shown that bacteria can induce local abnormalities in bone metabolism, playing a significant role in the formation of necrotic bone However, whether local bacteria in mandibular osteomyelitis can also lead to systemic abnormalities in bone metabolism is currently unknown. This study aims to elucidate the relationship between different pathogenic bacteria and various laboratory markers of systemic bone metabolism in mandibular osteomyelitis, based on the clinical characteristics and laboratory examination results of 34 confirmed cases at the First Affiliated Hospital of Xinjiang Medical University.

2. Manuscript Preparation

2.1 Case and Methods

2.1.1 Diagnostic criteria for suppurative mandibular osteomyelitis

Suppurative mandibular osteomyelitis is an infectious condition characterized by a predominantly suppurative inflammatory process affecting the medullary cavity, trabecular bone, cortical bone, and periosteum of the mandible and maxilla. It is primarily caused by odontogenic suppurative infections in both adults and children. Based on different etiological factors, it can be classified as odontogenic, traumatic, hematogenous, or secondary osteomyelitis. According to the route of infection occurrence spread, it can be categorized as central or marginal osteomyelitis. The disease course can be further

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divided into acute and chronic osteomyelitis [7].

2.1.2 Diagnosis criteria for drug-induced mandibular osteomyelitis

The diagnostic criteria for drug-induced mandibular osteomyelitis, as defined in the 2022 AAOMS guidelines, include: (1) History of past or current treatment with bisphosphonate medications.(2) Presence of bone exposure or necrosis in the oral and maxillofacial region, with a duration of the lesion lasting for at least 8 weeks. (3) Absence of previous radiation therapy to the oral and maxillofacial region or absence of evident metastatic bone disease in the mandible [8].

2.1.3 The diagnostic criteria for radiation-induced mandibular osteomyelitis

Radiation-induced mandibular osteomyelitis is a bone disorder characterized by inflammation and necrosis primarily affecting the jawbone tissue within the irradiated area. It is accompanied by damage to the surrounding soft tissues and persists for at least 3 months without spontaneous healing. Additionally, it is essential to exclude recurrence of primary tumors, medication-related bone disorders, and radiation-induced neoplasms in the mandibular tissues [9].

2.2 Study participants

According to the diagnostic criteria for mandibular osteomyelitis, data of 34 patients diagnosed with mandibular osteomyelitis, who were treated at the Department of Oral and Maxillofacial Surgery of the First Affiliated Hospital of Xinjiang Medical University from December 1, 2022 to May 1, 2023, were collected. All patient information was complete. With the patients' consent, bacterial sampling swabs were used to collect oral purulent fluid or other secretions for bacterial culture and identification before intravenous antibiotic administration. According to the etiology, the patients were classified into three groups: suppurative mandibular osteomyelitis, radiation-induced mandibular osteomyelitis, and medication-induced mandibular osteomyelitis.

2.3 Statistical methods

Data organization was carried out using Excel 2010, and statistical analysis of the data was performed using SPSS 27.0 software. Fisher's exact test was employed for qualitative data, whereas independent samples t-test and one-way analysis of variance (ANOVA) were used for quantitative data that satisfied the normal distribution assumption. A significance level of $p<0.05$ was considered as indicating a significant difference.

2.4 Results

2.4.1 The general information

In 34 cases, the age of patients ranged from 20 to 83 years old. Among them, there were 6 cases below the age of 40, 16 cases above the age of 60, and 12 cases between the ages of 40 and 60. Among the 34 patients, there were 15 males and 19 females. Regarding the etiology of jaw osteomyelitis in these patients, 17 cases (50%) were attributed to suppurative causes, 8 cases (23.5%) to radiation-induced causes, and 9 cases (26.5%) to medication-related causes. The comparison between age and the etiology of jaw osteomyelitis revealed no statistically significant difference ($p>0.05$, Table 1). Similarly, there was no statistically significant difference between gender and the etiology of jaw osteomyelitis ($p>0.05$).

Table 1: The comparison between age groups and the etiology of jaw osteomyelitis was conducted.

	classification of causes			P value
	suppurative	radiation-induced	drug-induced	
Age<40	5(83.3%)	0(0.0%)	1(16.7%)	0.1
40≤Age≤60	7(58.3%)	4(33.3%)	1(8.3%)	
Age>60	5(31.3%)	4(25.0%)	7(43.8%)	

2.4.2 Laboratory examinations

In 34 patients, a comparison of different etiological classifications and bone metabolism markers showed no significant differences ($p>0.05$, Table 2). However, in post hoc multiple comparisons, significant differences were observed between radiation-induced jaw osteomyelitis and drug-induced jaw osteomyelitis in terms of osteocalcin and calcium markers ($p<0.05$, Table 2). Furthermore, significant differences were found between suppurative jaw osteomyelitis and radiation-induced jaw

ISSN 2706-6819 Vol.5, Issue 10: 127-131, DOI: 10.25236/IJFM.2023.051020

osteomyelitis in terms of alkaline phosphatase marker (p<0.05, Table 2). No significant differences were observed among the three etiological classifications in other markers such as 25-hydroxyvitamin D, parathyroid hormone, and phosphate (p>0.05, Table 2).

Table 2: Comparison of different etiological classifications and bone metabolism markers.

	Osteocalcin (ng/mL)	25-Hydroxyvitamin D (nmol/L)	Parathyroid hormone (pmol/L)	alkaline phosphatase (U/L)	serum calcium (mmol/L)	serum phosphate (mmol/L)
suppurative	13.51±8.92	34.53±13.83	3.88±2.30	105.65±55.44b	2.18±0.12	1.19±0.19
radiation-induced	17.29±10.11**a**	35.96±11.80	5.06±1.82	64.44±19.40b	2.22±0.05c	1.25±0.13
drug-induced	8.51±3.06**a**	39.33±17.86	5.73±3.50	75.76±22.96	2.10±0.12c	1.06±0.27
F	2.5	0.319	1.653	3.066	3.061	1.91
P	0.099	0.729	0.208	0.061	0.061	0.165

Note: a indicates that the bone calcium levels are significantly different in multiple comparisons, with P<0.05; b indicates that the alkaline phosphatase levels are significantly different in multiple comparisons, with P<0.05; c indicates that the calcium levels are significantly different in multiple comparisons, with P<0.05.

According to the bacterial culture results, the 34 patients were divided into two groups: the oral normal flora group (18 cases) and the non-oral normal flora group (16 cases). There were no significant differences in bone metabolism indicators between the oral normal flora group and the non-oral normal flora group. (p>0.05, Table 3)

Table 3: The comparison of bone metabolism indicators between the oral normal flora group and the non-oral normal flora group.

	Osteocalcin (ng/mL)	25-Hydroxyvitamin D (nmol/L)	Parathyroid hormone (pmol/L)	alkaline phosphatase (U/L)	serum calcium (mmol/L)	serum phosphate (mmol/L)
Oral normal flora	12.41±7.68	36.11±15.36	4.78±2.82	91.63±51.66	2.15±0.11	1.18±0.23
Non-Oral normal flora	14.91±10.84	36.23±11.54	4.27±2.11	78.08±15.18	2.22±0.11	1.16±0.17
F	1.659	0.498	0.381	3.015	0.032	0.021
P	0.207	0.486	0.542	0.092	0.859	0.886

Table 4: Comparison of different etiological classifications and bacterial culture results.

	classification of causes			P value
	suppurative	radiation-induced	drug-induced	
Oral normal flora	13(52.00%)	4(16.00%)	8(32.00%)	0.232
Non-Oral normal flora	4(44.40%)	4(44.40%)	1(11.10%)	

Comparing different etiological classifications and bacterial culture results, there were no significant differences among the three different etiological classifications in terms of bacterial culture results (p>0.05, Table 4).

In the comparison of bacterial culture results with age, there were no significant differences between the oral normal flora group and the non-oral normal flora group across different age groups (p>0.05, Table 5).

Table 5: Comparison of bacterial culture results with age.

	classification of causes			P value
	Age<40	40≤Age≤60	Age>60	
Oral normal flora	5(20.00%)	8(32.00%)	12(48.00%)	0.776
Non-Oral normal flora	1(11.10%)	4(44.40%)	4(44.40%)	

In the comparison of age with bone metabolism markers, a significant difference was observed in the parathyroid hormone index (p<0.05, Table 6). Post hoc multiple comparisons revealed a significant difference in the parathyroid hormone index between patients aged <40 years and those aged >60 years (p<0.05, Table 6). A significant difference in the calcium index was observed between patients aged 40≤age≤60 and those aged >60 years (p<0.05, Table 6). No significant differences were found in the remaining markers across different age groups (p>0.05, Table 6).

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Table 6: Comparison of age groups with bone metabolism markers.

	Osteocalcin (ng/mL)	25-Hydroxyvitamin D (nmol/L)	Parathyroid hormone (pmol/L)	alkaline phosphatase (U/L)	serum calcium (mmol/L)	serum phosphate (mmol/L)
Age<40	16.87±12.28	32.18±14.93	2.66±0.78**a**	97.14±48.70	2.16±0.08	1.24±0.14
40≤Age≤60	11.82±5.16	39.27±11.02	4.13±1.89	79.57±21.44	2.23±0.12**b**	1.20±0.18
Age>60	12.59±9.10	35.29±16.44	5.77±3.03**a**	90.98±56.98	2.13±0.11**b**	1.12±0.25
F	0.739	0.532	4.045	0.353	2.686	0.971
P	0.486	0.593	0.027	0.705	0.084	0.39

Note: a indicates a significant difference in parathyroid hormone in post hoc multiple comparisons ($p<0.05$); b indicates a significant difference in calcium in post hoc multiple comparisons ($p<0.05$)

3. Conclusion

Our study found that there was a significant association between different age groups and the etiological classification of jaw osteomyelitis. The proportion of suppurative jaw osteomyelitis was found to be higher in younger age groups, while the proportion of radiation-induced and medication-related jaw osteomyelitis increased with age. This suggests that most cases of osteomyelitis in young individuals are attributed to dental bacterial infections, while elder individuals with a history of malignancy are more likely to develop osteomyelitis as a result of previous radiotherapy or chemotherapy. However, the statistical analysis did not reveal a significant difference in the distribution of etiological classifications among different age groups, possibly due to limited sample size and resulting sampling bias.

No significant differences were observed in the comparison of etiological classifications and markers of bone metabolism. This could be attributed to the long-term use of anti-osteoporotic medications, such as bisphosphonates, which may inhibit bone resorption and subsequently decrease levels of bone alkaline phosphatase and calcium [10,11]. However, Toshihisa Komori [12] demonstrated in a study that bone alkaline phosphatase does not play a role in bone mass regulation; instead, its function is to guide the parallel alignment of hydroxyapatite crystals with collagen fibers.

There were significant differences ($p<0.05$) observed in the alkaline phosphatase levels between suppurative jaw osteomyelitis and radiation-induced jaw osteomyelitis, suggesting that radiation exposure may lead to a decrease in alkaline phosphatase levels due to damage to osteoblasts [13,14].

There were no significant differences observed in the comparison of bacterial culture results between normal oral flora and non-oral normal flora among different age groups. This may be attributed to the limited sample size. Additionally, no significant differences were found in the bone metabolism markers between normal oral flora and non-oral normal flora. These findings suggest that the type of bacteria may not be a significant factor influencing bone metabolism.

Significant differences were observed in the comparison of bone metabolism markers between patients aged <40 years and those aged >60 years, specifically in the parathyroid hormone (PTH) levels. Tianhong Chen [15] suggested that the bone-regulating mechanism of PTH involves T cells of the immune system, cells belonging to the osteoblastic lineage, and even intestinal microbiota. These findings indicate the complexity of PTH's bone-regulating mechanism, which might not be limited to the skeletal system alone but also involve immune and gastrointestinal systems. Age is associated with changes in immune function, which may influence PTH levels. Silvano Adami [16] demonstrated that the relationship between PTH and 25-hydroxyvitamin D is regulated by age and calcium intake. Caroline Robersson [17] reported a case of jaw osteomyelitis in an adolescent girl that completely resolved in the affected area shortly after initiating treatment with a gonadotropin-releasing hormone analog. This suggests a close association between hormones and jaw osteomyelitis, indicating that hormonal therapy may potentially serve as a novel treatment modality for jaw osteomyelitis.

Significant differences were observed in the post hoc multiple comparisons of calcium levels between patients aged 40 to 60 years and those aged >60 years. This finding is attributed to the fact that as age increases, there is greater calcium loss, which is also influenced by calcium intake.

The isolation of specific bacteria from infected bone is greatly influenced by disease progression mechanisms, host comorbidities, and environmental exposure. Simply sampling and culturing microbial communities from pus samples may result in the inability to cultivate the corresponding bacteria. Therefore, more advanced research methods, such as 16S rRNA gene amplicon sequencing, should be employed to investigate bone tissue and determine the pathogens involved in osteomyelitis [18]. It is imperative to abandon outdated research methods that may impact the study and instead adopt more stable and advanced gene sequencing technologies. In the complex environment of the oral cavity, these approaches will provide greater insights into the role of bacteria in various forms of

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osteomyelitis and their influence on bone metabolism.

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