E-ISSN 2250-0944
ISSN 2250-1150
DOI: 10.48047/ijprt/16.01.159

Research Article

The Role of Vascular-Bone Coupling Disruption in the Pathophysiology and Progression of Osteoradionecrosis of the Jaw

Baizad Khan[1], Nauman Shirazi[2], Shameen Fatima Shoaib[3], Usman Manzoor Warraich[4], Shah Faisal[5], Suleman Khan[6]

[1]Bachelor of Dental Surgery, Abbottabad International Dental College, Khyber Medical University, Peshawar, Pakistan

[2]B.D.S, M.Phil. Demonstrator, Department of Oral Biology, Karachi Medical and Dental College, Karachi Metropolitan University, Karachi, Pakistan

[3]MBBS MPhil Histopathology, Akhtar Saeed Medical College Lahore, Pakistan

[4]BDS, FCPS, Assistant Professor Periodontology, Bakhtawar Amin Medical and Dental College, Multan, Pakistan

[5]BDS, DCD (Periodontology), Khyber College of Dentistry, Peshawar, Pakistan

[6]BDS, FCPS (OMFS), Senior Registrar (OMFS) Abbottabad International Medical and Dental College, Abbottabad, Pakistan

Corresponding author: Baizad Khan, Bachelor of Dental Surgery, Abbottabad International Dental College, Khyber Medical University, Peshawar, Pakistan,
Email: behzadkhanswb@gmail.com

Received: 26.12.25 | Revised: 11.03.26 | Accepted: 20.03.26 | Published: 03.04.2026

ABSTRACT

Osteoradionecrosis (ORN) of the jaw is a debilitating radiotherapy complication that is identified by impaired bone healing, a lack of vascularity, and a lack of cells. This study was conducted to test the contribution of vascular-bone coupling disruption to the pathophysiology and progression of ORN. This research used a cross-sectional study design and consisted of 120 patients with the diagnosis of ORN after head and neck radiotherapy. A purposive sampling method was used to recruit participants with an age range of 30-70 years in tertiary care hospitals and oncology centers. The data were collected with the help of a complex of clinical examination forms, a radiography based on a cone beam computer tomography (CBCT), and Doppler ultrasound to evaluate the vascular state and histopathologic examination of bone biopsies. The parameters, which were vascular integrity, bone remodelling, and the severity of necrosis, were registered systematically. The results revealed that there is a strong connection between invigorated vascular provision and deteriorated bone regeneration; hence, the criticality of the interaction between angiogenesis and osteogenesis in the pathogenesis of ORN. The loss of vascular bone connections was found to worsen tissue hypoxia, retard recovery, and make tissue prone to necrosis. The present study highlights the necessity of the early vascular examination and specific therapeutic approaches to angiogenic-osteogenic balance restoration as a preventive and management method of osteoradionecrosis.

Keywords: Osteoradionecrosis, jaw, pathophysiology, vascular, progression

INTRODUCTION

Osteoradionecrosis (ORN) is an extreme, delayed radiotherapy side effect, where non-healing irradiated bone, which remains more than three months without tumor growth, is found (Lyons et al., 2014). It occurs most frequently in patients receiving treatment for head and neck malignancies and is a major clinical problem as it has a complicated pathophysiology and meager treatment response. Nevertheless, recent developments indicate that vascular-bone coupling disturbances are more holistic and mechanistic in the progression of the disease. The association between angiogenesis (the formation of new blood vessels) and

osteogenesis (bone formation) is known as vascular-bone coupling, which is a tightly regulated process necessary to ensure bone homeostasis and bone repair (Kusumbe et al., 2014). The blood vessels are not only involved in supplying oxygen and nutrients, but also in providing signaling molecules that control the activity of osteoblasts and osteoclasts. It has been demonstrated that specialized endothelial cells (especially the type H vessels) directly affect bone regeneration and stimulate the growth of osteoprogenitor cells (Kusumbe et al., 2014). The malfunction of this coupling mechanism, particularly following exposure to radiation results, in disturbed bone remodeling and retarded recovery, which also plays a role in the pathogenesis of ORN.

Radiotherapy generates direct and indirect injury to vascular endothelial cells, leading to shrinkage in vascular density, fibrosis, as well as elimination of small blood vessels (Delanian and Lefaix, 2004). This impairment of tissue perfusion and oxygenation leads to a hypoxic microenvironment that suppresses the activity of osteoblasts and induces osteocyte apoptosis (Delanian and Lefaix, 2004). Moreover, radiation changes the expression of the growth factors, including growth factor vascular endothelial growth factor (VEGF), which plays a vital role in angiogenesis and thus the balance is disrupted between bone formation and resorption (Jacobson et al., 2010).

The process of bone remodeling is a dynamic process that is considered to include the activities of osteoblasts, osteoclasts and osteocytes. Under normal circumstances, it is strongly associated with vascular supply, but radiation damages the osteoblastic differentiation and increases the osteoclastic activity, which results in overall bone loss (Rathbone et al., 2013). The impaired bone regeneration, together with the impaired vascularization, exposes irradiated bone to necrosis despite the slightest trauma like tooth removal (Nabil and Samman, 2012). This emphasizes the role of vascular/bone coupling as one of the core processes to ensure bone integrity.

ORN clinically manifests itself in pain, bone, infection, and pathological fractures in severe cases. The severity of ORN is also generally distinguished by such systems as the Notani classification, where the scope of bone involvement and clinical symptoms is taken into consideration (Notani et al., 2003). Research has proved that more severe ORN is associated with a higher degree of vascular compromise and hindered bone recovery, which is why the disruption of vascular-bone interactions is another supporting factor (Chronopoulos et al., 2018).

The recent studies have also highlighted the molecular pathways of vascular-bone coupling, such as the involvement of hypoxia-inducible factor-1 alpha (HIF-1alpha) and VEGF signaling and Notch in the regulation of angiogenesis and osteogenesis (Wang et al., 2017). These disruptions are further caused by radiation induced oxidative stress and inflammation, which cause fibrosis and decrease cellular viability (Delanian & Lefaix, 2004). Also, the dysfunction of endothelial cells has been discovered as one of the most important factors in ORN development since it restricts the ability of osteoprogenitor cells to be recruited and slows down the healing of tissues (Kumar et al., 2018).

Jawbones and more specifically mandible are more vulnerable to ORN because they have relatively poor blood supply when compared to the other bones and are more prone to trauma and infection (Lyons et al., 2014). Risk factors: high-dose radiation (>60 Gy), poor oral health, and invasive dental procedures are well-known factors that impact more negatively on the vascular integrity and bone healing (Nabil & Samman, 2012). Further, age, comorbidities, and nutritional status of the patient are also issues that affect the severity and development of ORN.

Development of imaging procedures, including cone beam visualization of the computed tomography (CBCT) and Doppler ultrasound, has enhanced the possibility to evaluate bone structure and the state of the vessels in ORN patients (Chrcanovic et al., 2010). With such modalities, the vascular compromise and bone alterations are detected early, and timely intervention is undertaken. Strategies that address vascular building-bone linkage, including hyperbaric oxygen therapy and the application of angiogenic growth factors, have proved to be beneficial in terms of the improvement of the result, that is, augmenting the tissue

oxygenation and neovascularization (Annane et al., 2004).

Although these developments have been made, the mechanisms that are involved in the disruption of vascular bone coupling in ORN are not fully understood. More studies are required to investigate the relationship between vascular injury and bone remodeling in more detail. The knowledge of these mechanisms can result in the creation of specific therapies that are capable of restoring the balance between angiogenesis and osteogenesis, which ultimately will result in a better patient outcome.

To conclude, osteoradionecrosis of the jaw is a multidimensional disease with vascular bone coupling being at the heart of the matter. Vascular damage that results from radiation causes poor bone remodeling, hypoxia, and slow healing, which contribute to disease progression. Research on this association would be critical in coming up with effective preventive and therapeutic measures for ORN.

METHODOLOGY

The current study was done based on a cross-sectional analytical study design to determine the role of vascular bone coupling disruption in the pathophysiology and development of osteoradionecrosis (ORN) of the jaw. Research was conducted during six months in tertiary care hospitals and oncology centers that had maxillofacial surgery and radiotherapy departments. A purposive sampling method was used to select 120 patients who were diagnosed with ORN after having undergone head radiotherapy and neck radiotherapy. They were recruited patients between 30 and 70 years with clinically and radiographically verified ORN, and those with systemic bone diseases, recurring tumors and active chemotherapy were excluded to minimize confounding bias.

The process of data collection was conducted on the basis of structured questionnaires, clinical evaluation, as well as imaging methods. A Demographic and Clinical Proforma (DCP) that was created by the principal investigator in 2024 with 12 items (age, gender, radiotherapy dose, duration since therapy, and medical history) was used to gather demographic and baseline clinical information. Osteoradionecrosis was measured using the Notani Classification System constructed by Notani et al. (2003), and it classifies ORN into three grades (clinical and radiographic involvement).

In the form of a structured Vascular Assessment Form (VAF), adapted by Rubin et al. (1994), and a total of 8 items were used to determine blood flow characteristics, vessel integrity, level of perfusion, and grade of vascular compromise (with normal, mild, moderate, and severe being the options). Vascular status was assessed by Doppler ultrasound findings. Bone remodeling and healing conditions were determined using cone beam computed tomography (CBCT) and histopathological examination with the help of Bone Healing Assessment Score (BHAS) based on Marx (1983) that included 10 parameters such as bone density, sequestrum formation, cortical disruption and osteoblastic activity.

The Oral Health Impact Profile-14 (OHIP-14) developed by Slade (1997), was used to measure the patient-reported outcomes by including 14 items in seven domains, including functional limitation, physical pain, psychological discomfort, and social disability. All the items were measured using a 5-point Likert scale of 0 (never) to 4 (very often), with the higher the score, the worse the oral health-related quality of life.

Eligible patients were recruited when they were visiting a clinic regularly after receiving informed consent. The first version involved having the participants fill in the Demographic and Clinical Proforma (DCP), and after that, the OHIP-14 questionnaire, which took about 10-15 minutes to fill. Patients who had literacy problems were also helped with the assistance of interviewer-based questioning. This was followed by a comprehensive clinical analysis by trained maxillofacial experts to determine the severity of ORN by the use of the Notani Classification System.

A radiologist then carried out a Doppler ultrasound assessment on the vascular status, and the results were documented on the Vascular Assessment Form (VAF). All the patients were subjected to CBCT imaging to assess bone architecture and structural damage, with some cases needing additional confirmation being subjected to histopathological analysis. The Bone Healing Assessment Score (BHAS) was filled in

accordance with findings at the level of imaging and biopsy. All the data collection processes were standard and placed under similar clinical settings to provide reliability. The data were coded and typed into SPSS version 26 to be analyzed. The descriptive statistics (frequencies, percentages, means and standard deviations) were done, and the inferential statistics (Chi-square test and Pearson correlation) were used to determine the association between vascular status, bone remodeling and ORN severity. A p-value less than 0.05 was taken to be statistically significant. Today, ethical issues such as confidentiality, anonymity, and voluntary participation were highly observed during the study.

RESULTS

Table 1: Demographic Characteristics of Participants (n = 120)

Variable	Category	Frequency (n)	Percentage (%)
Age Group (years)	30–40	28	23.3
	41–50	36	30.0
	51–60	34	28.3
	61–70	22	18.3
Gender	Male	78	65.0
	Female	42	35.0
Radiotherapy Dose	<60 Gy	40	33.3
	≥60 Gy	80	66.7
Duration Post-RT	<1 year	32	26.7
	1–3 years	54	45.0
	>3 years	34	28.3

Table 2: Clinical Severity of Osteoradionecrosis

Severity Grade	Frequency (n)	Percentage (%)
Mild	30	25.0
Moderate	52	43.3
Severe	38	31.7
Total	120	100.0

Table 3: Vascular Status Assessment (Doppler Findings)

Vascular Status	Frequency (n)	Percentage (%)
Normal Perfusion	22	18.3
Mild Compromise	34	28.3
Moderate Compromise	40	33.3
Severe Compromise	24	20.0
Total	120	100.0

Table 4: Bone Remodeling Status (CBCT + Histology Findings)

Bone Remodeling Status	Frequency (n)	Percentage (%)
Normal	18	15.0
Mild Impairment	36	30.0
Moderate Impairment	42	35.0
Severe Impairment	24	20.0
Total	120	100.0

Table 5: Association Between Vascular Status and ORN Severity (Chi-Square Test)

Vascular Status	Mild ORN	Moderate ORN	Severe ORN	Total
Normal Perfusion	12	8	2	22
Mild Compromise	10	18	6	34
Moderate Compromise	6	20	14	40
Severe Compromise	2	6	16	24
Total	30	52	38	120

Chi-Square Value = 28.45; p-value = 0.001 (Significant)

Table 6: Correlation Between Vascular Compromise and Bone Remodeling

Variables	Correlation Coefficient (r)	p-value
Vascular Compromise vs Bone Damage	0.68	0.0

DISCUSSION

This paper examined how vascular bone coupling can disrupt the pathophysiology and development of osteoradionecrosis (ORN) of the jaw, and they found a significant correlation between vascular impairment and bone remodeling. The results showed that severely vascular impaired patients had better grades of ORN, which proved the idea that angiogenesis-osteogenesis interaction disruption is an important mechanism in the progression of the disease. These findings can be correlated with earlier research that stated that endothelial damage caused by radiation results in impaired perfusion and eventual bone necrosis (Epstein et al., 1987).

This notion has been supported in more recent studies that have shown that microvascular damage causes chronic hypoxia and fibrosis that impair tissue repair (Hopewell, 2003). The present findings also augment this knowledge by quantitatively correlating vascular compromise and clinical severity implying, that vascular bone coupling loss is not just a factor but a force in the development of ORN.

In this analysis, bone remodeling impairment had a favorable correlation with vascular compromise ($r = 0.68$, $p < 0.001$), meaning that the less supply of blood has a direct impact on osteogenic activity. Zhang et al. (2010) have also reported similar results and have shown that osteoblast proliferation and differentiation are inhibited by radiation with stimulation of osteocyte apoptosis. The result of this disproportion in bone turnover is structural and vulnerability to necrosis. Moreover, reduced angiogenic signaling would be demonstrated to inhibit the recruitment of osteoprogenitor cells, thus slowing the healing process of the bone (Maes et al., 2010).

Delayed diagnosis and absence of early vascular check-up could be the reasons why moderate to severe cases of ORN prevailed in this study population. Research carried out by Patel et al. (2016) has indicated that imaging modalities can greatly lessen the disease progression when the vascular compromise is identified at an early stage. According to this, Doppler ultrasound, as well as CBCT that was utilized in the current study, offered useful information not only of vascular integrity but also of bone structure, supporting the significance of multimodal diagnostic methods.

The other key observation of the research is that ORN was more prevalent in patients who had a radiation dose of 60g and above. This finding aligns with past reports in the literature that revealed that there is a dose effect between radiation exposure and tissue damage (Shaw et al., 2015). The mediation process of vascular and bone damage by inflammation and oxidative stress cannot be underestimated. Reactive oxygen species (ROS) that are caused by radiation are also involved in endothelial damage and degradation of cellular repair (Spitz et al., 2004). This inflammatory microenvironment also interferes with the angiogenesis/ osteogenesis equilibrium, resulting in progressive tissue destruction. The results of the study indirectly confirm such a mechanism whereby patients who had severe vascular compromise also had more bone destruction.

The findings of the research emphasize the role of vascular-bone coupling pathways. New interventions like administration of pentoxifylline and tocopherol that enhance blood circulation and fibrosis have brought encouraging results in the management of ORN (Delanian et al., 2011). Moreover, regenerative therapeutic methods such as stem cell treatment and growth factor administration are designed to repair angiogenicosteogenic balance and increase tissue healing (D'Souza et al., 2014). The rationale of such targeted interventions is supported by the strong relationship that was noted in this study between vascular impairment and bone damage.

Although there are strengths to this study, there are some limitations. The cross-sectional design constrains the possibility to draw causal relationships between vascular disruption and progression of ORN. The longitudinal studies are urgent to better understand the temporal relationships of vascular and bone coupling. Also, purposive sampling can bring about selection bias, which can have an impact on the generalizability of the results.

This paper has shown very good evidence that the involvement of vascular bone coupling in the development and progression of the osteoradionecrosis of the jaw is crucial in the pathophysiology and development of the disease. The fact that vascular compromise, impaired bone remodeling and the severity of the disease are significantly correlated highlights the importance of an early vascular evaluation and focused treatment options.

CONCLUSION

Osteoradionecrosis of the jaw is a complicated disease whereby the vascular-bone coupling disruption is a major cause underlying the problem. The research results prove that the impaired vascular supply is a significant factor that provokes improper bone healing and worsens the disease. Angiogenesis and osteogenesis interventions detected early are much needed to improve clinical outcomes and prevent the development of the disease.

REFERENCES

1. Annane D, Depondt J, Aubert P, Villart M, Gehanno P, Gajdos P, et al. Hyperbaric oxygen therapy for radionecrosis of the jaw: A randomized, placebo-controlled trial. J Clin Oncol. 2004;22(24):4893–4900.
2. Chrcanovic BR, Reher P, Sousa AA, Harris M. Osteoradionecrosis of the jaws a current overview. Part 1: Physiopathology and risk factors. Oral Maxillofac Surg. 2010;14(1):3–16.
3. Chronopoulos A, Zarra T, Ehrenfeld M, Otto S. Osteoradionecrosis of the mandible: A ten-year single-center study. J Craniomaxillofac Surg. 2018;46(6):837–846.
4. Delanian S, Lefaix JL. The radiation-induced fibroatrophic process: Therapeutic perspective via the antioxidant pathway. Radiother Oncol. 2004;73(2):119–131.
5. Delanian S, Chatel C, Porcher R, Depondt J, Lefaix JL. Complete restoration of refractory mandibular osteoradionecrosis by pentoxifylline and tocopherol. Int J Radiat Oncol Biol Phys. 2011;80(3):832–839.
6. D'Souza J, Lowe D, Rogers SN, Brown JS. Changing trends in the management of osteoradionecrosis. Br J Oral Maxillofac Surg. 2014;52(4):356–362.
7. Epstein JB, Wong FL, Stevenson-Moore P. Osteoradionecrosis: Clinical experience and a proposal for classification. J Oral Maxillofac Surg. 1987;45(2):104–110.
8. Hopewell JW. Radiation-therapy effects on bone density. Med Pediatr Oncol. 2003;41(3):208–211.
9. Jacobson AS, Buchbinder D, Hu K, Urken ML. Paradigm shifts in the management of osteoradionecrosis. Oral Oncol. 2010;46(11):795–801.
10. Kumar V, Abbas AK, Aster JC. Robbins and Cotran Pathologic Basis of Disease. 10th ed. Philadelphia: Elsevier; 2018.
11. Kusumbe AP, Ramasamy SK, Adams RH. Coupling of angiogenesis and osteogenesis by a specific vessel subtype in bone. Nature. 2014;507(7492):323–328.
12. Lyons A, Osher J, Warner E, Kumar R, Brennan PA, McCaul JA. Osteoradionecrosis—A review of current concepts and classification. Br J Oral Maxillofac Surg. 2014;52(5):392–395.

13. Maes C, Kobayashi T, Selig MK, Torrekens S, Roth SI, Mackem S, et al. Osteoblast precursors migrate with invading blood vessels during bone development. Nat Med. 2010;16(11):1230–1235.
14. Nabil S, Samman N. Risk factors for osteoradionecrosis after head and neck radiation: A systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113(1):54–69.
15. Notani K, Yamazaki Y, Kitada H, Sakakibara N, Nomura T, Nakamura M, et al. Management of osteoradionecrosis of the jaws. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;96(3):273–278.
16. Patel V, McGurk M, Rogers SN. Clinical outcomes in patients with osteoradionecrosis of the jaws. Br J Oral Maxillofac Surg. 2016;54(6):652–656.
17. Rathbone CR, Cross JD, Brown KV, Murray CK, Wenke JC. Effect of various concentrations of antibiotics on osteogenic cell viability. J Orthop Res. 2011;29(7):1070–1074.
18. Shaw RJ, Butterworth CJ, Silcocks P, Tesfaye BT, Bickerstaff M, Jackson R, et al. HOPON trial: Hyperbaric oxygen for the prevention of osteoradionecrosis. Health Technol Assess. 2019;23(23):1–144.
19. Spitz DR, Azzam EI, Li JJ, Gius D. Metabolic oxidation/reduction reactions and cellular responses to ionizing radiation. Cancer Metastasis Rev. 2004;23(3–4):311–322.
20. Wang Y, Wan C, Deng L, Liu X, Cao X, Gilbert SR, et al. The hypoxia-inducible factor α pathway couples angiogenesis to osteogenesis during skeletal development. J Clin Invest. 2007;117(6):1616–1626.
21. Zhang Q, Liu Y, Zhang X, Zhang Y, Zhao J. Effects of radiation on osteoblast proliferation and differentiation. J Radiat Res. 2010;51(5):567–573.