Problems, Management and Benefits of Changes in Altitude Affecting the Maxillofacial Region: Literature Review

Kismanto[1], Wawan Muyawan[2], Andri Rezano[3], Bambang Pontjo Priosoeryanto[4], Harmas Yazid Yusuf[5]

1. Doctoral Programme Faculty of Dentistry, Padjadjaran University, Indonesia.
2. Department of Community Medicine, Indonesia University, Indonesia.
3. Departement of Biomedical Sciences, Division of Cell Biology, Faculty of Medecine, Padjadjaran University, Indonesia.
4. Division of Veterinary Pathology, School of Veterinary Medicine and Biomedical Sciences, IPB University, Bogor, Indonesia.
5. Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Padjadjaran University, Indonesia.

Abstract

Increasing height causes a decrease in air pressure, temperature and partial oxygen. Changes in air pressure around the body will cause it to have a physiological disorder, including in the maxillofacial region. Problems frequently occurring in the maxillofacial region due to changes in altitude are barosinusitis, otitis media and barodontalgia (aerodontalgia). These disorders occur as a result of gas trapped into spaces in the maxillofacial region. Changes in air pressure do not only cause disorders, but with good management they can also provide benefits to the body, especially to the maxillofacial region. Intermittent hypoxia is a form of hypoxia that may have a beneficial impact on health, especially the health of the maxillofacial region.

The purpose this article is to find out problems that often occur in the maxillofacial region and its management as a result of changes in altitude as well as identify their benefits for health, especially for the maxillofacial region.

As a conclusion, correct diagnosis and proper care will reduce the occurrence of barodontalgia/aerodontalgia. Intermittent hypoxia can improve the bone healing process through upregulation of HIF-1α expression and VEGF enhancement.

Review (J Int Dent Med Res 2023; 16(3): 1348-1354)

Keywords: Air pressure, intermittent hypoxia, barodontagia, hypoxia inducible factor-1α, Vascular endothelial growth factor.

Received date: 17 June 2023 **Accept date:** 16 August 2023

Introduction

Humans are destined to live on the earth's surface through all their lives. The mechanism of the human body systems is physiologically conditioned to function normally at a certain sea level with the air pressure of 760 mmHg (101,3 kPa).[1] Changes in air pressure around the body will result in physiological disorders of the body. As altitude increases air pressure, temperature and partial oxygen pressure decreases.[2]

The human body consists of many cavities including in the maxillofacial region. These parts of the body are directly affected by changes in altitude. As the height increases the air pressure is getting lower making the volume of air in the cavities of the body rise, which may cause pain in the ear (barotitis media), in the sinus (barosinusitis) and in the teeth (barodontalgia/aerodotalgia).[3] As altitude increases partial oxygen pressure also decreases. A condition in which the inspired oxygen level is falling may result in hypoxia, i.e. a state in which the supply of the oxygen (O_2) to the body tissue is decreasing up to below the physiological level despite adequate oxygen perfusion to the tissue by blood.[4]

As altitude increases, air pressure falls resulting in changes in volume of gas. This conforms with the Boyle's law which states that at the same temperature the volume of gas is inversely proportional to its pressure.[1] If its pressure decreases, the volume of the gas increases and vice versa. An altitude of higher than 9.000 ft is the point that causes disorders whether it is acute or subacute. A height of above 10.000 ft is the point resulting in physiological changes.[5]

Corresponding author:
Kismanto,
Doctoral Programme Faculty of Dentistry, Padjadjaran University, Indonesia.
E-mail: kismantokapen@gmail.com

A term that is used to refer to disorders caused by changes in air pressure around human body is "Dysbarism", which occurs in cavities and beyond capabilities of the body to adapt so it pressure/suction on the mucosa located on the wall of the cavities. Dysbarism includes decompression sickness, nitrogen narcosis, high-pressure neurological syndrome, barotrauma and arterial gas embolism.[6] A disorder occuring during or immediately following changes in air pressure surrounding the body that is caused by the gas trapped in a cavity or by the gas entering the blood vessel is called decompression sickness. The etiology of decompression is divided into 2 categories: "Trapped Gas" or gas developing in a cavity of the body and "Evolved Gas" or the sublimation of gas dissolving in the liquid of the body. The gas develops in cavities of the body that have narrow passages. These cavities may include sinus paranasalis, cavum tympani, tractus digestivus, lungs and teeth that are decayed or not treated properly.[7]

Hypoxia does not always make a bad impact on the body. Hypoxic conditions at the level and duration that can be tolerated such as intermittent hypoxia will exert an advantageous effect such as increased cell resistance against exposure to the next hypoxia. It is used as a non-pharmacological therapy in the acceleration of the bone fracture healing process. [8,9]

All mammalian cells need oxygen to work and survive and to ensure adequate oxygen supply tissues and cells have developed a strategy for adapting to conditions with insufficient oxygen supply called hypoxia. The cellular oxygen sensor serves to measure oxygenation changes in tissues and then draw responses to restore oxygen supply as needed. Genetic adaptation to hypoxia is controlled by HIF-1α. This HIF-1α complex will be immediately formed when there is a stimulus resulted from hypoxia. HIF-1α is a part of HIF, which is the main transcriptional regulator of the cellular response caused by hypoxia.[10,11] Under hypoxic conditions, hydroxylation process of HIF-1α does not occur so HIF-1α molecule is not recognized by the von hippel-lindau (VHL) protein and is not degraded. Then the amount or concentration of HIF-1α will increase to enable HIF-1α to enter the nucleus of the cell and bind to the aryl hydrocarbon receptor nuclear translocator (ARNT) in the hypoxic response element (HRE). This binding will then activate genes responding to hypoxia such as vascular endothelial growth factor (VEGF).[12] VEGF is a vascular endothelial growth factor which serves an important mediator during the angiogenesis process, where angiogenesis always precedes osteogenesis. VEGF has the potential to increase Bone Morphogenetic Protein (BMP) which plays a role in bone formation.[13,14]

This article is written with the aim of revealing problems that often occur in the maxillofacial region due to changes in air pressure and their management as well as identifying their benefits for health, especially for the maxillofacial region.

Materials and methods

This review was conducted based on guidelines for writing a literature review for a journal. [15,16]

Search Strategy

The search was restricted to articles published from 2009 to 2022 to find out novelty of evidence. This study used a search method within databases of reputable journals in ScienceDirect and Pubmed about changes in altitude and their impacts on maxillofacial and intermittent hypoxia. Keywords used in the search were "altitude", "barodontalgia" and "intermittent hypoxia" but articles in any languages other than Indonesian and English were excluded. The search generated 37 articles that may serve as reference in this systematic review.

Eligibility assessment

The first step was identifying articles, then screening and checking duplication and the relevance of the title and abstract. The articles were excluded if they were not relevant to the topic, purpose, and population of this study. This step was followed by assessment of the quality of the study and data extraction. The final step was to synthesize selected articles.

Results

Problems in the Maxillofacial Region

Barotrauma

Barotrauma is a tissue damage caused by a pressure difference between spaces of air in the human body and its surrounding fluids, which occur during flying, diving or when undergoing a

hyperbaric oxygen therapy.[17] Barotrauma is divided into two categories: facial barotrauma and dental barotrauma.[18] Barotrauma may cause damages to the maxillofacial region including the middle ear, paranasal sinuses, nose and teeth.[17,19,20] These changes in pressure may also trigger inflammation, oedema, bleeding in the the middle ear, and may even cause intracranial complications that develop symptoms of dizziness and severe pain in the face.[21,22]

Barodontalgia (Aerodontagia)

Barodontalgia is a pain in a tooth caused by changes in air pressure.[20] The incidence of barodontalgia usually begins from an altitude of 2.000ft to 5.000ft.[23] Barondontalgia is ranked number 5 as a disorder caused by changes in altitude. During 1980s the incidence of barodontalgia in a chamber was reported to reach 0.26%. Zadik and Einy reported that the pain caused by barodontalgia during flight was due to new tooth restoration (26.9%), sinusitis (18.5%), tooth or bone infections (18,5%) and pulp necrosis (18%-36%).[17]

Dental disorders that may result in barodontalgia includes caries (acute pulpitis, chronic pulpitis and pulp necrose), poor dental fillings, periapical abcess, periodontitis, periodontal packets, tooth impaction and retention cyst.[24] Barodontalgia is mostly caused by dental caries that extend into dentine and pulps resulting in inflammation called pulpitis. An acute pain felt when the plane is ascending may be caused by reversible pulpitis while an udentified discomfort occuring when the plane is climbing may be due to irreversible pulpitis. A pain bore when the plane is travelling downward may be resulted from pulp necrosis while a discomfort felt either when the plane is ascending or descending may be caused by an abcess or cyst.[21,23]

Changes in barometric pressure may lead to dental fracture (odontocrexis). Leaky fillings or secondary caries may cause fracture when there are sudden changes in pressure. When placing dental prosthesis, especially full denture, problems occur due to the retention of the prosthesis which is based on atmospheric pressure, attachment and gravitation so that lower pressure may cause disruption to the retention of the prosthesis. Fillings may break due to variation of contraction of materials for fillings caused by changes in temperature. Changes in pressure develops periodontal infections and dry mouth cavities (xerostomia) and hypo-salivation which may form caries.[5,18,21,24,25,26] Continuous hypoxia in the long term may induce loss of cortical alveolar bones, reduce the volume of *intra radicular* bones, xerostomia and even inferior alveolaris nerves paresthesia may occur due to baro trauma[17,27]

Benefits of Changes in Altitude

Intermittent hypoxia (IH) is a hypoxic condition occuring for a certain period that is intersperesed with normoxia. Exposure to intermittent hypoxia develops results in a mechanism of adaptation to anticipate hypoxia at the cellular and systemic levels. The hypoxia inducible factor 1 (HIF-1) gene is a transcription factor that plays a vital role as a regulator of gene expression in a condition of low oxygen level (hypoxia). The HIF 1 gene regulates homeostasis of oxygen and glucose metabolism. It induces transcription of proteins that are required for adaption to hypoxia.[28] Intermittent hypoxia is classified according to its severity, its duration in one period, number of periods and accumulated length of expsosure.[8]

Intermittent hypoxia has been recognized to be able to provide many benefits since the advantages of HIF-1 gene were identified by numerous studies. Exposure to hypoxia increases the accumulation of HIF-1α in cells, HIF-1α spurs the activation of several growth factors such as VEGF which will increase the process of angiogenesis which is needed in wound healing.[29] A therapeutic method using a local HIF-1α gene is proven to improve osseointegration in dental implants. HIF-1α has an effect of a basic protein that can stimulate osteogenesis and angiogenesis.[30] Both osteogenesis and angiogenesis are phenomena of the relationship between HIF-1α and VEGF in the healing process of periodontal ligamentum.[31] Administration of 0.2 ml of HIF-1α (4μg of HIF-1α DNA mixed with 100μg of Hph-1-GAL4 at room temperature) into a tooth socket after extraction have shown that the formation of bone becomes significantly faster in 4 weeks after extraction.[32] Activation of HIF-1 may serve as the protector against apical periodontitis through regulation of NF-κB, proinflammatory cytokines, M1 macrophages and osteoclasts osteogenesis.[33] .

The IH exposoure can increase the bone healing process. It is proven by the increase of bone formation, bone mass, and bone power. IH increase the bone healing process through the

increse of HIF-α which plays a regulator role of the genes expression in the hypoxia condition.[34] Chronic intermittent hypoxia is proven to increase expression of HIF-1a protein. Modest hypoxia (9-16% inspired O_2) and low cycle count (3-15 episodes/day) may exert beneficial effects without pathological consequences. Intermittent hypoxia at a prescribed dose is an efficient strategy to accelerate bone fracture healing through upregulation of HIF-1α expression. This proves that HIF-1α plays a key role in angiogenic and osteogenic processes.[9,35, 36,37,38]

Discussion

Pathophysiology of Problems in the Maxillofacial Region

The altitude that often triggers a pain begin from the height of 5,000 ft to 15,000 ft. Pain in certain teeth and for certain people is usually felt at a fixed altitude on every flight. The pain may become stronger or wear off as the altitude increases, but will go if the altitude gets lower and usually disappears at the altitude where the pain begins.[17] Headache is a common symptom of altitude sickness. Headaches are commonly located in the frontal, temporal but mostly bilateral part and the pain caused is usually dull. A person with a history of headaches will most likely feel the pain at a certain altitude.[19] Headaches, paresthesias or toothaches in the maxillary posterior teeth may be resulted from barosinusitis or barodontalgia.[20]

Barodontalgia may occur when the air pressure decreases, increases or remains the same even when the pressure returns to normal.[20] The tooth that causes barodontia is exceptionally difficult to detect because changes in altitude do not happen in clinical conditions.[17] Barodontalgia always occurs in decayed teeth or defective dental fillings which result in a cavity that has a narrower opening. Predisposing factors for barodontalgia are dental disorders with acute exacerbations such as exposed pulps, pulpal necrosis and acute or chronic pulpitis, crown fractures, erosion, acute periapical abscess, odontogenic infections and secondary caries, and defective dental fillings.[5,8]

Changes in pressure may cause movement of fluid from the exposed tooth into the dental pulp. Experiments with animals have demonstrated that changes in air pressure induces movement of fluid from the dentin into the pulp chamber after enamel preparation. Retrospective studies have shown that clinical manifestations of barodontalgia are found in caries or damaged fillings in the dentine area.[20] Barodontalgia may also lead to oral pathology such as paresthesia of the inferior alveolar nerves, cyst expansion accompanied by loss of sense of taste. The faster the change in altitude the greater is the change in barometric pressure. This condition will induce faster cyst expasion. The results of the study show that the longer the nerves are under pressure, the longer the latency period for recovery will result.[17]

The connection between nasal cavities and adjacent sinuses allows pressure changes in the sinuses to be compensated for. Changes in intranus pressure that cannot be compensated for may result in mucosal injury leading to sinusitis.[39] Changes in altitude are usually accompanied by changes in temperature that becomes colder. This condition may lead to epistaxis, which is drying of the nasal mucosa causing small blood vessels to burst.[19] Inside the ear there is the eustachian tube that serves to balance the air pressure from outside and the air pressure inside the human body. Sudden changes in air pressure either when the altitude increases or decreases will diminish the function of the eustachian tube, so it will induce symptoms such as pain in the ear, hearing loss, tinnitus and vertigo.[7,40]

Management

Immediate treatment for barodontagia is simple, which is by returning patients to their initial altitude before the illness occurs. If the pain occurs when they are climbing or reaching a certain altitude, descending will ease the pain. If the discomfort is felt when they are descending then going up again will relieve the pain. After dental treatment & other surgical treatment that last for more than 7 days patient are advised not dive or fly in non pressurized cabins for the next 24 hours.[41] Options of treatment for barodontalgia are numerous, depending on the major symptoms, clinical findings and diagnosis. This treatment may range from palliative to definitive.[42]

Management of acute barosinusitis symptoms resulting from the use of antibiotics, decongestants and oral steroids can be treated with decongestants and analgesics immediately after an incident. The use of antibiotics and steroids is considered for symptoms that persist

for 24 hours.[39] Treatment for barodontalgia for flight crew requires special considerations when planning restorative, endodontic and prosthodontic treatments and ental surgery. Preventive measures are crucial, such as periodic dental check-up, good dental restoration and temporary grounding if there is a pulp damage.[7,20]

Proper dental treatment can only be administered if an accurate diagnosis has been made. Panoramic examination can help establish diagnosis of asymptomatic dental disorders. In aerospace dentistry the use of resin cement as filling materials has become an option to ensure retention of restoration and prevent toothache by blocking dentinal tubules and inhibiting microleakage. In endodontic treatment, a 24-hour observation is required before flying.[17]

In the case of oral surgery, when performing a posterior extraction, the position of the oroantral fistula that may develop must be carefully considered to help reduce the possibility of sinusitis development while flying. To prevent post extraction complications a patient should not fly for 24-72 hours to allow time to relieve symptoms, stop pain medication and stabilize blood clots. In case an oroantral fistula develops, temporary grounding should be enforced on the patient until the fistula opening is completely closed because changes in pressure may delay the healing process.[17]

Temporary flying suspension is necessary for flight crew members when there is concern about their ability that might put the flight at risk. Unfavorable medical conditions as well as medicines taken may reduce their ability to operate an aircraft while in flight. Some drugs such as opiates may cause declining focus while some antibiotics may cause diarrhea. Moreover, medical conditions that require antibiotics treatment should become a reason for immediately imposing temporary suspension on flight crew.[17] Fédération Dentaire Internationale (FDI) has recommended against flying on a non-pressurized cabin aircraft after undergoing a dental treatment for the next 24 hours or 7 days after having a dental surgery.[42]

Therapeutic Potential of Intermittent Hypoxia

The use of low-dose intermittent hypoxia is regarded as a non-pharmacological approach and is a simple and safe method, including for bone fracture healing.[9] Angiogenesis and Osteogenic are essential in the process of bone development and growth as well as fracture healing because the formation of blood vessels is crucial in supplying nutrients, oxygen, growth factors, cytokines and osteoblasts and also osteoclast precursors. Osteogenesis is always preceded by angiogenesis. The process of bone formation and vascularization make a unity called "angiogenic-osteogenic coupling".[13,14]

Intermittent hypoxia has a positive effect on osteoblast differentiation, which plays a role in accelerating the healing process of bone fractures and increasing bone mass and strength as can be seen from an increase in bone volume, bone mineral density and trabecular number. Bone growth and remodeling is determined by the activity of osteoblasts.[35,36]

The body will naturally adapt to a hypoxic condition. Cells and tissues will respond to this condition with the activation of the hypoxia-inducible factor-1 (HIF-1), which is a transcriptional activator that is sensitive to decreased oxygen levels.[36] During hypoxia, HIF 1 serves as a trigger to express glycolytic enzymes, transport glucose across membranes, vascular grow factors and erythropoietin, which is a protein acting as a regulator of vascularization and life of cells. Intermittent Hypoxia that is properly managed provides numerous benefits.[28] Application of low-dose intermittent hypoxia in several periods is simple, safe and effective and is considered as a potential therapy for several clinical disorders.[9]

Benefits of intermittent hypoxia depend on variables that are used including 1) severity of hypoxia (e.g. degree of hypoxemia, often reported as percentage of inspired oxygen), 2) duration of hypoxia in several episodes, 3) number of hypoxia/reoxygenation cycles (episodes) per day; 4) presentation pattern (e.g, several episodes per day with periods of normoxia until the next day vs limited exposure episodes of three days per week, etc.); 5) cumulative duration of exposure (days/weeks/months); and 6) regulation of other relevant variables such as prevailing arterial carbon dioxide levels.[9]

The precise dose for clinical therapy has not been determined, but several doses have proved useful to treat disorders or diseases. Recurrent mild acute IH (3-5 minutes of 12-15%, HAI 2, 3-5 minutes normoxic interval, 5-9 episodes/day, 15 days) has a beneficial effect on

patients with chronic obstructive pulmonary disease (COPD). On the other hand, a more moderate IH protocol (10–12% O_2, 3 times/week, 3–6 weeks) has been reported to have an advatageous effect on metabolism, including weight loss, reduced cholesterol and blood sugar levels and improved insulin sensitivity. Intermittent Hypoxia (10 minutes, 13% O_2, 10-minute interval, 4 hours/day, 28 days) has a positive effect on mouse bone tissue, which is increasing phosphatase and osteoblast activities in bone tissue.[9] Several studies on the benefits of HIF-1 have raised hope that HIF-1 can be applied to the bone healing process in the maxillofacial region such as tooth extraction aftercare, bone fractures, dental implants and even to orthodontic treatment.

Conclusions

Problems brought by the effect of changes in altitude on the oral cavity, especially barodontalgia/aerodontalgia always begin with dental disorders or improper dental care. Correct diagnosis and proper care will minimize the occurrence of barodontalgia/aerodontalgia. Low-dose hypoxia that is appropriately managed provides many benefits for healing process although the correct dose still needs to be learned further.

Acknowledgements

The Authors would like to express our gratitude especially to the Centre of Millitary Dentistry Research, Padjadjaran University, for their support for this study.

Declaration of Interest

The authors declare that there are no conflicts of interest that could have appeared to influence this study.

References

1. Gradwell DP. The Earth's atmosphere. In: Gradwell DP, editor. Ernsting's Aviation and Space Medicine. 5th ed. Francis; 2016: p. 6–9.
2. Linawati L, Sitam S, Mulyawan W, et al. Effect of Intermittent Hypobaric Hypoxia Exposure on HIF-1α, VEGF, and Angiogenesis in the Healing Process of Post-Tooth Extraction Sockets in Rats [published online ahead of print, 2023 Jun 9]. Eur J Dent. 2023;10.1055/s-0043-1768639. doi:10.1055/s-0043-1768639.
3. Kamran B, Nakdimon I, Zadik Y. Military Aviation Dentistry. Refuat Hapeh Vehashinayim. 2017;34(2):42–7.
4. Gosling P. Dorland's illustrated medical dictionary. Australas Chiropr Osteopat. 2003;11(2):65.
5. Ashour AA. High Altitude and Its Effects on Oral Health: A Review of Literature. J Adv Oral Res. 2020;11(2):143–7.
6. Savioli G, Alfano C, Zanza C, Bavestrello Piccini G, Varesi A, Esposito C, et al. Dysbarism: an overview of an unusual medical emergency. Medicina (B Aires). 2022;58(1):104.
7. Scully C. Sports, travel and leisure, and pets. Scully's Med Probl Dent [Internet]. 2014;738–48. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7150042/
8. Dale EA, Ben Mabrouk F, Mitchell GS. Unexpected benefits of intermittent hypoxia: enhanced respiratory and nonrespiratory motor function. Physiology. 2014;29(1):39–48.
9. Navarrete-Opazo A, Mitchell GS. Therapeutic potential of intermittent hypoxia: a matter of dose. Am J Physiol Integr Comp Physiol. 2014;307(10):R1181–97.
10. Roach RC, Hackett PH, Wagner PD. Molecular Oxygen Sensing. In: Hypoxia Translation in Progress. New York: Springer; 2016: p. 247–9.
11. Drager J, Harvey EJ, Barralet J. Hypoxia signalling manipulation for bone regeneration. Expert Rev Mol Med. 2015;17:1–16.
12. Zimna A, Kurpisz M. Hypoxia-inducible factor-1 in physiological and pathophysiological angiogenesis: applications and therapies. Biomed Res Int. 2015;2015:1–13.
13. Rady AAM, Hamdy SM, Abdel-Hamid MA, Hegazy MGA, Fathy SA, Mostafa AA. The role of VEGF and BMP-2 in stimulation of bone healing with using hybrid bio-composite scaffolds coated implants in animal model. Bull Natl Res Cent. 2020;44(1):1–9.
14. Saran U, Piperni SG, Chatterjee S. Role of angiogenesis in bone repair. Arch Biochem Biophys. 2014;561:109–17.
15. Green BN, Johnson CD, Adams A. Writing narrative literature reviews for peer-reviewed journals: secrets of the trade. J Chiropr Med. 2006;5(3):101–17.
16. Gasparyan AY, Ayvazyan L, Blackmore H, Kitas GD. Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. Rheumatol Int. 2011;31:1409–17.
17. Yuce E, Koçer G, Çini TA. Current concepts of oral and maxillofacial rehabilitation and treatment in aviation. Gen Dent. 2016;64(5):44–8.
18. Rajpal PS, Sachdev G, Waghmare M, Pagare SS. Dental barotrauma and barodontalgia. J Med Sci Clin Res. 2014;2:3477–83.
19. Cingi C, Erkan AN, Rettinger G. Ear, nose, and throat eVects of high altitude. 2009;267:467–71.
20. Stoetzer M, Kuehlhorn C, Ruecker M, Ziebolz D, Gellrich NC, von See C. Pathophysiology of barodontalgia: a case report and review of the literature. Case Rep Dent. 2012;2012:1–4.
21. Lakshmi D. Aviation dentistry. J Clin diagnostic Res JCDR. 2014;8(3):288.
22. Džupová O, Beneš J. Air flight barotrauma and meningitis: causality seems real. J Laryngol Otol. 2020;134(2):184–6.
23. Nakdimon I, Zadik Y. Barodontalgia among aircrew and divers. Aerosp Med Hum Perform. 2019;90(2):128–31.
24. Sahu N, Naik D, Sahu S, Sahu KK. Barodontalgia: Dental Implications at High Altitudes. Indian J Forensic Med Toxicol. 2020;14(4):8245–9.
25. Shetty K, Manipal S, Mohan R, VV B. Aviation Dentistry: is it an Unexplored Field of Dentistry? A Cross-Sectional Study. J Aerosp Technol Manag. 2020;12:1–7.
26. Chitkara N, Garg A, Mittal R. Exploring Astronautical Dentistry: A Review. Int Healthc Res J. 2017;1(4):5–8.
27. Terrizzi AR, Fernandez-Solari J, Lee CM, Conti MI, Martínez MP. Deleterious effect of chronic continuous hypoxia on oral health. Arch Oral Biol. 2016;72:1–7.
28. Semenza GL. Hypoxia-inducible factors in physiology and medicine. Cell. 2012;148(3):399–408.
29. Khoswanto C. Hypoxia inducible factor 1α as key factor in wound healing post tooth extraction: An overview. J Int Dent Med Res. 2020;13(3):1191–7.
30. Zou D, He J, Zhang K, Dai J, Zhang W, Wang S, et al. The

bone-forming effects of HIF-1α-transduced BMSCs promote osseointegration with dental implant in canine mandible. PLoS One. 2012;7(3):e32355.
31. Oishi S, Shimizu Y, Hosomichi J, Kuma Y, Maeda H, Nagai H, et al. Intermittent hypoxia influences alveolar bone proper microstructure via hypoxia-inducible factor and VEGF expression in periodontal ligaments of growing rats. Front Physiol. 2016;7:416.
32. Lim H-C, Thoma DS, Jeon M, Song J-S, Lee S-K, Jung U-W. Effect of Hypoxia-Inducible Factor 1α on Early Healing in Extraction Sockets. Biomed Res Int. 2018;2018:1–9.
33. Hirai K, Furusho H, Hirota K, Sasaki H. Activation of hypoxia-inducible factor 1 attenuates periapical inflammation and bone loss. Int J Oral Sci. 2018;10(2):1–10.
34. Setiawan K, Setyaningsih A, Sari DN, Maulina T, Mulyawan W, Rezano A, et al. The Therapeutic Potentials of Intermittent Hypoxia on Bone Healing: A Systematic Review. J Int Dent Med Res. 2022;15(4):1838–44.
35. Zhang L, Jin L, Guo J, Bao K, Hu J, Zhang Y, et al. Chronic Intermittent Hypobaric Hypoxia Enhances Bone Fracture Healing [Internet]. Vol. 11, Frontiers in Endocrinology . 2021. Available from: https://www.frontiersin.org/article/10.3389/fendo.2020.582670
36. Qiao J, Zhou M, Li Z, Ren J, Gao G, Cao G, et al. Comparison of remote ischemic preconditioning and intermittent hypoxia training in fracture healing. Mol Med Rep. 2019 Mar;19(3):1867–74.
37. Chen W, Wu P, Yu F, Luo G, Qing L, Tang J. HIF-1α regulates bone homeostasis and angiogenesis, participating in the occurrence of bone metabolic diseases. Cells. 2022;11(22):3552.
38. Zhang D, Ren L. Development of hypoxia-inducible factor 1α in tissue engineered angiogenesis and osteogenesis [Abstract]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi (Chinese J reparative Reconstr Surg). 2016;30(4):504–8.
39. Vaezeafshar R, Psaltis AJ, Rao VK, Zarabanda D, Patel ZM, Nayak JV. Barosinusitis: Comprehensive review and proposed new classification system. Allergy Rhinol (Providence). 2017;8(3):109-117. doi:10.2500/ar.2017.8.0221
40. Claes J, Germonpre P, Van Rompaey V, Bourmanne E. Ear, nose and throat and non-acoustic barotrauma. B-ENT/Royal Belgian Soc Ear, Nose, Throat, Head Neck Surg [Leuven]-Leuven, 2005, currens. 2016;12(S26/1):203–18.
41. Praveena R. Pressure provoking pain-barodontalgia: an overview. 2021. WORLD J Pharm Pharm Sci. 2019;8(1):609–17.
42. Kini P V, Jathanna VR, Jathanna R V, Shetty K. Barodontalgia: etiology, features and prevention. HRPUB. 2015;3(2):35–8.