REVIEW ARTICLE

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Radiographic evaluation of the healing process of alveolar abscess through regulation of VEGF and angiogenesis

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ABSTRACT

Objectives: This review article aims to explain how the regulation of vascular endothelial growth factor (VEGF) and angiogenesis on alveolar abscess healing process evaluation using radiograph.

Review: The databases used in this review are Google Scholar, PubMed, and Science Direct. A total of 1280 search results appeared based on keywords. The search results were selected by title and abstract according to their relevance to the review topic. A total of 24 literatures were reviewed. The alveolar bone destruction is one of the signs of an inflammatory lesion in the alveolar bone. Bone damage that occurs in cases of the abscess will reduce the absorption of x-rays thereby giving a radiolucent appearance on radiographic examination. A radiographic examination is a supporting examination that can be used to develop the healing process. The processes of angiogenesis and osteogenesis of bone homeostasis will complement each other for the bone healing process, while VEGF is a growth factor that can increase the expression of BMPs and osteoblast differentiation so that the bone healing process can take place properly.

Conclusion: VEGF plays a significant role in both bone healing and regulation of vascular development and angiogenesis. However, excessive VEGF can also be harmful to the process of bone repair because it can stimulate the recruitment of osteoclasts. Therefore, VEGF regulation has an important role in apical abscess healing, and radiographic images that are quantitatively analyzed can be used to quantify this healing process.

Keywords: *VEGF, angiogenesis, abscess alveolar, healing process, radiograph*
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INTRODUCTION

The alveolar abscess is the most common inflammatory lesion of the mandibular and maxillary alveolar bone. Alveolars abscesses are radiolucent lesions that form in the bone near the apex of nonvital teeth and occur due to bacterial infection. After adequate debridement, disinfection, and obturation, the root canal will heal in many apical lesions but not all of them. Some lesions may take a while to heal. Since the healing of apical lesions entails the regrowth of bone in the damaged area, it is imperative to comprehend the osteogenic signals that initiate and control the apposition of new bone. In some situations, endodontic therapy administered intracanal to apical lesions is ineffective. Apical lesions serve as the host response's defensive mechanism. However, this defense results in the destruction of the apical bone around it. Bone destruction is one of the most important early warning signs of an apical lesion. The ultimate elimination of the bone defect caused by this inflammatory response is the main clinical indicator and tool used to monitor the healing of these lesions. Bone destruction that occurs in cases of the abscess will reduce the absorption of x-rays thereby giving a radiolucent appearance on radiographic examination. Radiographic examination is a supporting examination that can be used to develop the healing process.[1,2]

Healing starts in the related region as inflammation starts. When factors causing the endodontic infection are eliminated with endodontic treatment, inflammatory mediator production in periapical tissues stops. The body's regulating mechanisms deactivate the local mediators that are already present. Prior to the healing of a wound, this procedure occurs. Although factors that cause inflammation are clearly known, there is a relatively low level of knowledge of the factors and mechanisms that cause the process to stop. The effectiveness of histamine and anti-inflammatory cytokines like IL-4, IL-10, IL-13, and TGF-b are known to be dependent on the balance between cyclic AMP levels (adenosine monophosphate) and cyclic GMP (guanosine monophosphate) in the cell. Natural

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inhibitors of inflammatory mediators (opioids, somatostatin, and glucocorticoids) are also known to be dependent on this mechanism.[2]

The healing mechanism for apical periodontitis lesions after suitable non-surgical root canal treatment is as follows: fibrovascular granulation tissue formation, removal of necrotic tissue and dead bacteria by active macrophages, and repair or regeneration of the wounded tissue. Apical lesion healing mainly occurs with regeneration. Thus, the tissues can return to their original structures. Osteoblasts in the alveolar bone, bone marrow mesenchymal stem cells, and multipotent stem cells in periodontal ligament are the cells that work in periapical lesion healing.[3] The healing process occurs in several phases: inflammatory, proliferative, and remodeling. The alveolar abscess healing process is closely related to the soft and hard tissue regeneration process. Bone tissue regeneration is a mechanism centered on the interaction between the processes of angiogenesis and osteogenesis. The processes of angiogenesis and osteogenesis of bone homeostasis will complement each other for the bone healing process, while VEGF is a growth factor that can increase the expression of Bone morphogenetic proteins (BMPs) and osteoblast differentiation so that the bone healing process can take place properly.[4–6] Several studies on the effect of VEGF in the process of healing and bone regeneration have been carried out, based on this the authors are interested in conducting a literature study on the regulation of VEGF in the process of angiogenesis-related to the evaluation of the abscess healing process through radiographs.

REVIEW

The databases used in this review are Google Scholar, PubMed, and Science Direct. A total of 1280 search results appeared based on keywords. The search results were selected by title and abstract according to their relevance to the review topic as VEGF regulation on osteogenesis, angiogenesis, and radiographic evaluation of alveolar abscess healing process A. A total of 24 literatures were reviewed.

The establishment of a functional vascular system is crucial during organ development as well as during tissue repair. Blood vessels in bone provide calcium and phosphate, the components for mineralization, in addition to oxygen and nutrition. Additionally, it appears that blood arteries in the bone marrow play a significant role in acting as a habitat for both skeletal stem cells, which produce bone, and hematopoietic stem cells, which form blood. A prompt and coordinated angiogenic response is crucial for effective bone regeneration, which further demonstrates the relationship between angiogenesis and osteogenesis during the healing of abcess. Increasing knowledge of the cellular and molecular mechanisms controlling the angiogenic cascade may aid in the evaluation of abscess healing process.[7,8]

One of the foremost broadly considered angiogenic development components is VEGF, an endothelial cell-specific mitogen. VEGF proteins are discharged by cells included in skeletal advancement and repair, counting endothelial cell, macrophages, fibroblasts, smooth muscle cells, osteoblasts, and hypertrophic chondrocytes. Distinctive from bone improvement, the early organize of bone healing is characterized by hematoma arrangement, which has solid proangiogenic properties, predominantly due to the presence of VEGF. The importance of an appropriate VEGF-mediated stimulation of angiogenesis during bone healing is eminent, as inhibition of VEGF activity through treatment with a soluble VEGFR or VEGF antagonist resulted in impaired healing of bone defects in mice. VEGF leads to moved forward effective bone repair in both models. VEGF can impact bone recovery by influencing bone cells in a roundabout way or specifically. First, through its activity on Endothelial cells, VEGF induces the angiogenic process. Bone-forming precursor cells possibly migrate concomitantly with these blood vessels to the bone callus defect, where they differentiate into osteoblasts. Secondly, through an angiocrine mechanism then VEGF can stimulate Endothelial cells to produce osteogenic cytokines that promote the differentiation of progenitor cells into osteoblasts. Lastly, VEGF may also directly influence osteoblast function. Accordingly, osteoblasts produce VEGF and respond to VEGF itself, which regulates chemotaxis, proliferation, and differentiation of osteoblasts.[8]

Apical abscess radiographically presents a round or oval radiolucent lesion with diffuse borders. In addition, the surrounding trabecular pattern will show a gradual transition from a normal pattern to an abnormal bone pattern.[9,10] X-ray absorption will decrease in abscess conditions due to bone destruction, so the image seen on the radiograph is radiolucent, whereas if an abscess heals, the bone matrix will be formed and the level of fibrous density will change, thereby increasing x-ray absorption. The condition of bone matrix density will affect the film layer, namely silver bromide (AgBr) so that changes in the radiographic pattern can be assessed by performing image processing on the radiograph.[11,12]

The process of bone repair after an injury takes place quickly and efficiently. Cellular and molecular mechanisms of bone repair or bone regeneration occur in several overlapping phases, namely the inflammatory phase, the proliferative phase, the soft callus formation phase, the cartilage bone replacement phase and the remodeling phase. The process that occurs after the formation of an alveolar abscess is inflammation of the infected area, then neutrophils will gather in that area. This process is followed by the entry of macrophages into the area and eating dead neutrophils and increasing the angiogenic response and initiating the healing process, with the invasion of these new blood vessels mesenchymal osteochondral

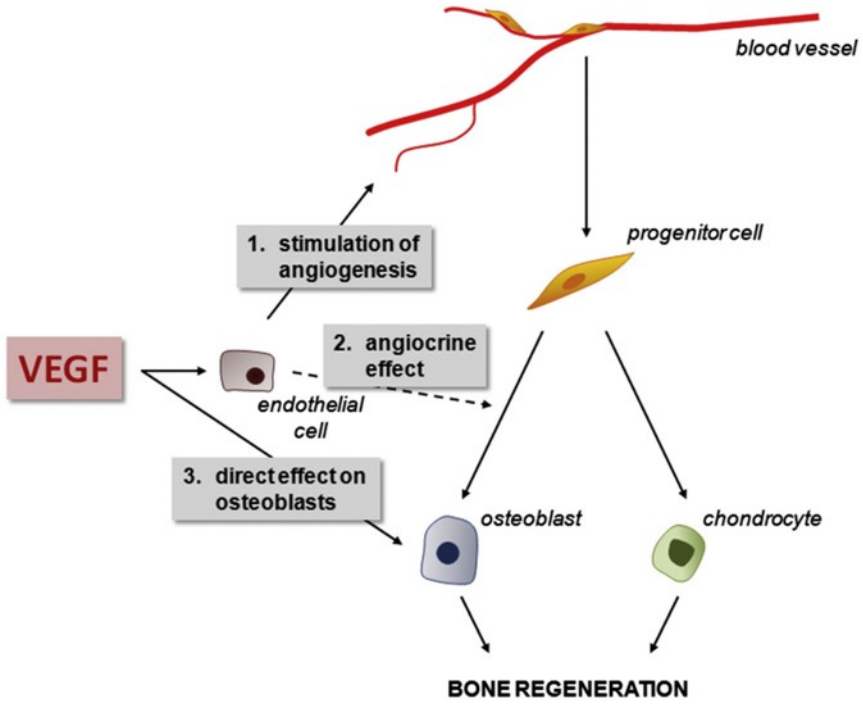

Figure 1. VEGF signaling during bone regeneration. VEGF stimulates the formation of new blood vessels, which can bring progenitor cells for bone formation. VEGF upregulates the expression of osteogenic growth factors in endothelial cells, mediating osteoblast differentiation[8]

progenitors will migrate to the area of infection where later these cells will proliferate and differentiate into osteoblasts. or chondrocytes, depending on the stability of the vascular supply, eventually the woven bone formed will gradually be remodeled into lamellar bone.[13,14]

VEGF one of the important growth factors in the regulation of vascular development and angiogenesis, but it also has an important role in bone repair because the processes of angiogenesis and osteogenesis are closely related. VEGF acts in both endochondral and intramembranous ossification processes, besides acting as a very important mediator during this process, not only in angiogenesis but also in various aspects of bone repair, such as chondrocyte differentiation, osteoblast differentiation, and osteoclast recruitment.[15]

VEGF is concentrated in the area of injury and contributes to the recruitment of macrophages or monocytes in the inflammatory phase. In the process of endochondral ossification in the process of bone repair, VEGF stimulates the recruitment of osteochondroprogenitor cells, induces cartilage, and stimulates cartilage resorption and its replacement with bone. Intramembranous ossification also depends on signals from VEGF, because this VEGF can increase the formation of bone mineralization in the area of bone that is affected by injury and besides that VEGF also regulates the maturation and differentiation of osteoclasts, so VEGF is needed in the bone repair process. VEGF acts on adjacent endothelial cells as an intermediary for angiogenic processes, where this process is very important in the process of maintaining vascular integrity and bone mass. In addition, intracellular VEGF in osteoblasts also regulates the balance of osteoblasts.[5,16]

VEGF is involved in various aspects of osteoblast function. Two studies have demonstrated a level-dependent chemoattractive effect of VEGF on human primary osteoblasts and human mesenchymal progenitor cells. In addition to its effect on cell migration, VEGF stimulates cell proliferation by up to 70%. It was also found that VEGF directly promotes primary osteoblast differentiation in vitro by increasing nodule formation and alkaline phosphatase activity. In addition, low levels of VEGF were found in the early process of osteoblast differentiation and continued to increase and then reached maximum expression during the mineralization period. Thus, VEGF has an important role in the regulation of bone remodeling by stimulating osteoblast differentiation.[15,17]

Intramembranous ossification is one of two processes that are important in the formation of bone tissue structure. Intramembranous ossification occurs in the formation of the flat bones of the skull, mandible, maxilla, and clavicle. It is also an important process in normal bone healing. Bone is formed from connective tissue such as mesenchymal tissue, not from cartilage. Intramembranous ossification occurs in several stages, namely the formation of an ossification center, calcification, formation of trabeculae, and development of the periosteum. Cells that are important in the formation of bone tissue through intramembranous ossification are mesenchymal stem cells, these cells will initiate intramembranous ossification and are non-specialized cells, whose morphology has characteristics that change as they develop into osteoblasts. VEGF increases

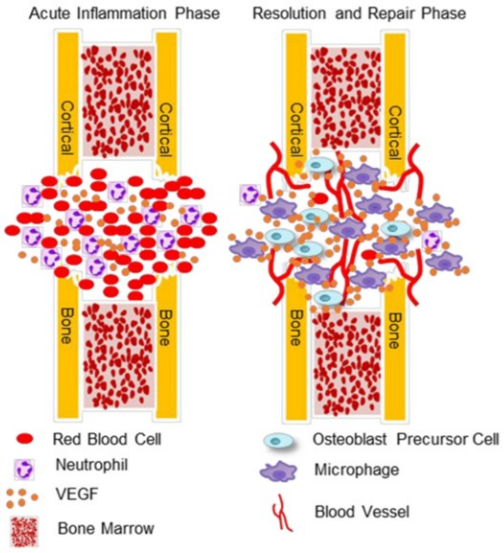

Figure 2. Expression and functions of VEGF in the inffammation phase during bone repair[18]

neovascularization, which in turn increases the number of mesenchymal cells in perivascular connective tissue. VEGF also stimulates vascular endothelial cells to secrete growth factors and cytokines that influence the differentiation of mesenchymal cells to enter the osteogenic process and be involved in osteogenesis. Bone repair is a process consisting of several steps involving migration, proliferation, differentiation and activation of several cell types. This repair process is very complex and involves various growth factors including VEGF.[15,19]

The process of intramembranous ossification depends on a merger of angiogenesis and osteogenesis. VEGF plays an important role in this process, stimulated by hypoxia during inflammation, osteoblasts release several factors including VEGF through HIF-1α. VEGF can act through its receptors on endothelial cells to induce angiogenesis, thereby increasing the supply of oxygen and nutrients needed for osteogenesis. Increased vascularity can stimulate bone stem cells and pre-osteoblasts and increase levels of osteogenic growth factors such as BMP2 and BMP4 as well as anabolic signals to further trigger osteoblast differentiation and mineralization. During bone repair, VEGF levels greatly affect the results, so too low levels of VEGF can interfere with bone and blood vessel relationships, whereas too much VEGF can also be detrimental to the bone repair process because osteoblastic maturation and mineralization can be inhibited through VEGFR2 signaling or it can be caused by the recruitment of osteoclasts that resorb new bone formation.[18]

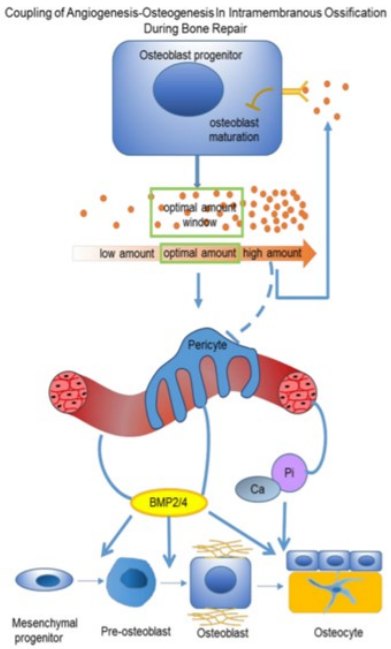

Figure 3. The role of VEGF in angiogenesis-osteogenesis during intramembranous ossification bone repair[18]

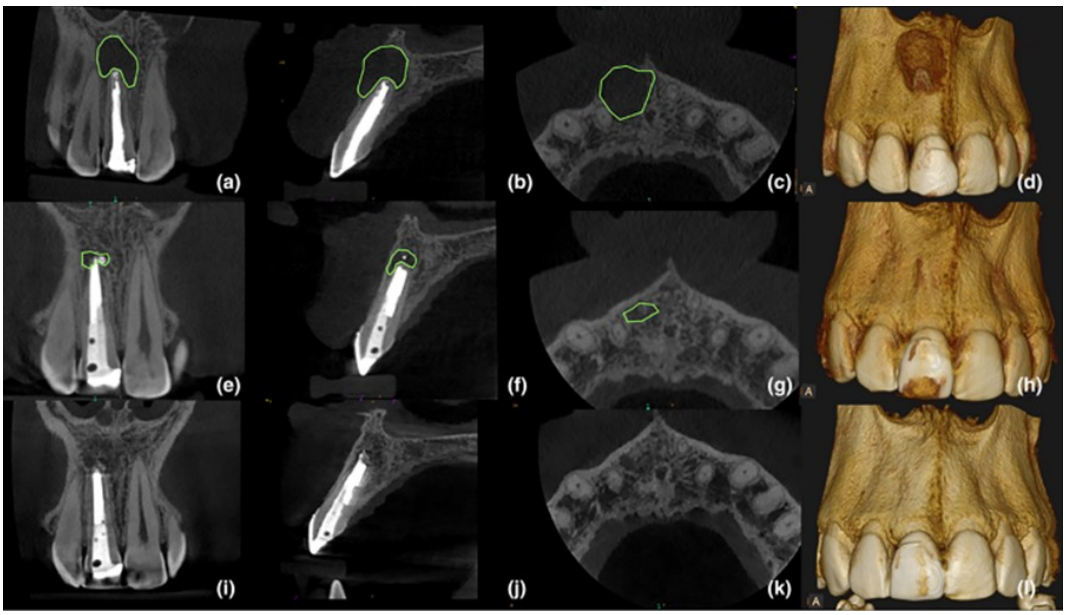

Figure 4. CBCT images of periapical bone healing on alveolar abscess[25]

The anatomical structure of bones on radiographs is very interesting and important to study because these images can be used as an aid in diagnosing and evaluating bones. Therefore, several studies have been carried out to identify most of the structures seen on intraoral and extraoral radiographs. The structure of the alveolar bone has attracted the attention of several researchers because it gives rise to various interpretations. The internal aspect of the alveolar bone has several terms such as cancellous, medullary, spongy, and trabecular bone. Researchers and clinicians assumed the lattice-like pattern on intraoral radiographs to represent the internal area of the medullar bone cavity. Trabecular bone has an 8-fold higher turnover than cortical bone and is more responsive to the body's metabolic responses. This is a very important phenomenon because the maxilla and mandible are rich in trabecular bone.[20]

The healing process of the apical abscess will cause the bone matrix to increase and the level of fibrous density will change, thereby increasing the absorption of x-rays which causes changes in the radiographic pattern. Changes in the pattern on this radiograph can be assessed qualitatively or quantitatively. Quantitative assessment results in a more objective assessment when compared to qualitative assessments that are only assessed visually because interpreting visually does not always identify all bone destruction that occurs. To date, many methods have been used to analyze the quality of alveolar bone. In the quantitative assessment of abscess healing, the process of changing radiographic patterns can be assessed using the bone texture morphometric analysis method which is a method of mathematically processing digital radiographic images with the help of software.[17,21–24]

CONCLUSION

The process of bone repair after an injury proceeds fast and effectively. Due to the tight relationship between the processes of angiogenesis and osteogenesis, VEGF plays a significant role in both bone healing and regulation of vascular development and angiogenesis. Additionally, VEGF induces the release of cytokines and growth factors by vascular endothelial cells, which influence the differentiation of mesenchymal cells to enter the osteogenic process and participate in osteogenesis.VEGF levels during bone repair have a significant impact on the outcomes. However, excessive VEGF can also be harmful to the process of bone repair because it can stimulate the recruitment of osteoclasts, which resorb newly formed bone, or it can hinder osteoblastic maturation. Therefore, VEGF regulation has an important role in apical abscess healing, and radiographic images that are quantitatively analyzed can be used to quantify this healing process.

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FOOTNOTES

All authors have no potential conflict of interest to declare for this article.

REFERENCES

1. Metzger Z, Kfir A. Healing of Apical Lesions: How Do They Heal, Why Does the Healing Take So Long, and Why Do Some Lesions Fail to Heal? Disinfect. Root Canal Syst. Treat. Apical

Periodontitis. 2014;15:297–318.
2. Tartuk GA, Bulut ET. The effects of periapical lesion healing on bone density. Int. Dent. Res. 2020;10:90–9.
3. Kaya S, Yavuz I, Uysal I, Akkuş Z. Measuring bone density in healing periapical lesions by using cone beam computed tomography: a clinical investigation. J Endod. 2012;38(1):28-31.
4. Devescovi V, Leonardi E, Ciapetti G, Cenni E. Growth factors in bone repair. Chir Organi Mov. 2008;92(3):161-8.
5. Liu Y, Berendsen AD, Jia S, Lotinun S, Baron R, Ferrara N, Olsen BR. Intracellular VEGF regulates the balance between osteoblast and adipocyte differentiation. J Clin Invest. 2012;122(9):3101-13.
6. Zhang H, Kot A, Lay YE, Fierro FA, Chen H, Lane NE, Yao W. Acceleration of Fracture Healing by Overexpression of Basic Fibroblast Growth Factor in the Mesenchymal Stromal Cells. Stem Cells Transl Med. 2017;6(10):1880-93.
7. Gómez-Gaviro MV, Lovell-Badge R, Fernández-Avilés F, Lara-Pezzi E. The vascular stem cell niche. J Cardiovasc Transl Res. 2012;5(5):618-30.
8. Stegen S, van Gastel N, Carmeliet G. Bringing new life to damaged bone: the importance of angiogenesis in bone repair and regeneration. Bone. 2015;70:19-27.
9. White SC, Pharoah MJ. Oral Radiology-E-Book: Principles and Interpretation. Elsevier Health Sciences; 2014.
10. Jaswal S, Patil N, Singh MP, Dadarwal A, Sharma V, Sharma AK. A Comparative Evaluation of Digital Radiography and Ultrasound Imaging to Detect Periapical Lesions in the Oral Cavity. Cureus. 2022 Oct 8;14(10):e30070.
11. Huang CC, Chen JC, Chang YC, Jeng JH, Chen CM. A fractal dimensional approach to successful evaluation of apical healing. Int Endod J. 2013;46(6):523-9.
12. Fitriandari BQ, Pramanik F, Adang RAF. Proses penyembuhan lesi periapikal pada radiografi periapikal menggunakan Software Image J. Padjadjaran J. Dent. Res. Students. 2018;2:116–24.
13. Claes L, Recknagel S, Ignatius A. Fracture healing under healthy and inflammatory conditions. Nat Rev Rheumatol. 2012;8(3):133-43.
14. Gómez-Barrena E, Rosset P, Lozano D, Stanovici J, Ermthaller C, Gerbhard F. Bone fracture healing: cell therapy in delayed unions and nonunions. Bone. 2015;70:93-101.
15. Yang YQ, Tan YY, Wong R, Wenden A, Zhang LK, Rabie AB. The role of vascular endothelial growth factor in ossification. Int J Oral Sci. 2012;4(2):64-8.
16. Hu K, Olsen BR. Osteoblast-derived VEGF regulates osteoblast differentiation and bone formation during bone repair. J Clin Invest. 2016;126(2):509-26.
17. Diomede F, Marconi GD, Fonticoli L, Pizzicanella J, Merciaro I, Bramanti P, Mazzon E, Trubiani O. Functional Relationship between Osteogenesis and Angiogenesis in Tissue Regeneration. Int J Mol Sci. 2020;21(9):3242.
18. Hu K, Olsen BR. The roles of vascular endothelial growth factor in bone repair and regeneration. Bone. 2016;91:30-8.
19. Jin SW, Sim KB, Kim SD. Development and Growth of the Normal Cranial Vault : An Embryologic Review. J Korean Neurosurg Soc. 2016;59(3):192-6.
20. Amer ME, Heo MS, Brooks SL, Benavides E. Anatomical variations of trabecular bone structure in intraoral radiographs using fractal and particles count analyses. Imaging Sci Dent. 2012;42(1):5-12.
21. Soğur E, Baksı BG, Gröndahl HG, Sen BH. Pixel intensity and fractal dimension of periapical lesions visually indiscernible in radiographs. J Endod. 2013;39(1):16-9.
22. Huang B, Wang W, Li Q, Wang Z, Yan B, Zhang Z, Wang L, Huang M, Jia C, Lu J, Liu S, Chen H, Li M, Cai D, Jiang Y, Jin D, Bai X. Osteoblasts secrete Cxcl9 to regulate angiogenesis in bone. Nat Commun. 2016;7:13885.
23. Ballmer-Hofer K. Vascular Endothelial Growth Factor, from Basic Research to Clinical Applications. Int J Mol Sci. 2018;19 (12):3750.
24. Saeed S, Ibraheem UM, Alnema M. Quantitative analysis by pixel intensity and fractal dimensions for imaging diagnosis of periapical lesions. Int. J. Enhanc. Res. Sci. Technol. Eng. 2019;3:138–44.
25. Mosquera-Barreiro C, Ruíz-Piñón M, Sans FA, Nagendrababu V, Vinothkumar TS, Martín-González J, Martín-Biedma B, Castelo-Baz P. Predictors of periapical bone healing associated with teeth having large periapical lesions following nonsurgical root canal treatment or retreatment: A cone beam computed tomography-based retrospective study. Int Endod J. 2024;57(1):23-36.