Genetic Association Of Hypoxia Inducible Factor (HIF) – 1 Alpha Gene And Residual Ridge Resorption Of Jaw Bone

Research Article

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Abstract

The residual ridge is exposed to constant bone resorption by considerable alterations between persons. In certain circumstances, this can cause disproportionate bone deterioration, making restorative dental management difficult. This inimitable curative procedure in the oral cavity is affected by specific factors in the oral tissue. HIF expression is diverse in oral wound restoration associated to that of skin wounds. The target of this review article was to look at a cistrontic connotation among SNP of the HIF-1 α gene that is understood to possess great genetic diversity, and also the residual ridge reabsorption (RRR). Hence, this review concentrates on the association and genetic basis of HIF α gene in residual ridge resorption.

Keywords: HIF-1; Single Nucleotide Polymorphisms; Residual Ridge Resorption.

Introduction

The extraction of a tooth is one of the most common dental treatments. Owing to the abridged mechanical filling of the tooth and the dental ligament after the tooth extraction, the residual ridge continues a process of continuous bone resorption [1]. The destroyed tissue integrity is restored within the first week, active bone formation begins, and the freshly formed bone gradually fills the socket over the next six months. Catabolic remodelling of the remaining ridge alveolar bone, on the other hand, occurs and is most rapid in the first six months, but it slows down over time [2].

Relatively little is known about the pathophysiology of residual ridge resorption. The magnitude of decrease is associated of a mix of structural, physiological, and mechanical factors. Because the residual ridge is mostly made up of distinct oral soft tissue and alveolar bone that forms as a consequence of tooth extraction wound healing, faults in cavity matrices production or cellular ac-

tivity can cause the residual ridge to deteriorate will lead to stalled healing [3]. As a consequence, RRR can be caused by genetic regulatory factors that disturb the feature and measure of bone by modifying the genetic pattern. When a tooth is pulled, blood vessels in the extraction socket are damaged, blood flow is cut off, and the oxygen pressure in the nearby region drops, resulting in tissue hypoxia [4, 5]. The homeostasis of oxygen in cells and in the body is largely controlled by the oxygen-inducible factor-1, or HIF-1. It is a critical mediator of oxygen-dependent genes and some of the genes that HIF-1 targets are well defined [6].

In dentistry, residual ridge (RR) refers to the clinical alveolar ridge even after the healing of the bone and tissues around the tooth has been achieved. During the first six months, resorption of the enduring ridge is speedy; afterwards, the bone resorption endures at a slower rate for the rest of the person's lifespan, causing in the loss of a great measure of the jaw construction. Atrophic residual ridges have always been an obstacle for a successful prosthodontic treatment [7]. This distinctive phenomenon has been defined

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as the residual ridge resorption (RRR). RR has major nutritional, aesthetic, anatomic, functional and prosthetic implications. There is no complete understanding of the etiology of residual ridge resorption. It might be due to specific cytokines and genetic variations in each individual [8].

Genetic factors were recognized recently since single nucleotide polymorphisms (SNPs) in genes involved in RRR have been identified in patients who have the condition. Researchers have found a strong correlation between genes affecting periodontal healing and the loss of residual ridges. The studies of SNPs in genes associated with alveolar bone health may provide useful information about its etiology, define the risk and offer new targets for treating the illness [9]. Literature search revealed only very few studies that addressed the genetic factors that are implicated in the inter individual variability of RRR development [10].

Genetic association of residual ridge resorption

Numerous efforts were made to learn more about the pathophysiology of resorption of the continuous residual ridge, but still no noteworthy results were found.

The quantifiable comparison of the persistent Residual ridge resorption, on the other hand, reveals significant variability among people under similar conditions, implying a possible genetic link. It is reinforced by massive literature evidence that genetic factors are highly associated with periodontitis, osteoporosis, and residual ridge resorption. However, the role of genes is essentially discussed in all the above studies [11]. It is necessary to explore the genetic factors affecting ridge resorption, so as to determine whether this may be intervened with the function of genes in causing resorptive alterations is complicated and fascinating [7]. While there is evidence on the effect of numerous genes engaged in producing many pathological variations in residual ridge resorption, a significant amount of study still needs to be conducted with respect to genetic variables involved in developing and leading to progressive alterations. Almost every illness in humans is impacted explicitly or implicitly by genetic variability, which confers vulnerability, tolerance, or interaction with environmental variables [12].

The most frequent kind of genetic variation is single nucleotide polymorphism (SNP), which occurs when an alternative base occurs at a frequency greater than 1% in the world population [9]. Song and Lee investigated the relationship between SNPs in vascular endothelial growth factor and residual ridge resorption (RRR) in 120 Korean patients with edentulous mandibles, finding a clear link among rs1570360 and haplotype A-C-C and RRR [13]. The investigations indicate it as a novel genetic marker for identifying people at risk of austere RRR following tooth extraction. Furthermore, AlSheikh *et al.*, discovered both a relationship among SNPs in the IL10 and NOD2 genes, and also that the genotypes of the various SNPs influence health and bone resorption in a study [14]. Discovering SNPs in susceptible genes would thus not only help us to get a better information of disease processes and their associated consequences, but it would also pave the way for more effective RRR therapy options.

The significant genes

In the mission to expose the role of genetic factors in the pro-

gress of RRR, there has been few reports which examined SNPs in different genes, with cytokine and growth factor genes, genes of matrix metalloproteinases (MMPs), fibroblast growth factor receptor (FGFR1), and hypoxia-inducible factor-1 (HIF-1 α) and have presented noticeable relations among certain polymorphisms and RRR. Sundar *et al.*, discovered a genetic link between SNPs in the matrix metalloproteinase-1 (MMP-1) gene promoter and RRR in the edentulous jaw [12].

HIF alpha gene SNP in residual ridge resorption

The Hypoxia-Inducible Factor (HIF)-1 protein complex is a dimeric protein complex which plays a significant role throughout the body's reaction to low oxygen concentrations, often known as hypoxia. HIF-1 is one of the major genes involved in homeostasis, which can promote vascularization in hypoxic regions such as localised ischemia and tumours. HIF-1 is a transcription factor for hundreds of target genes; also it is required for immune responses and is a key physiological regulator of homeostasis, vascularization, and anaerobic metabolism. HIF-1 contains of α and β subunits. The alpha subunit, which controls HIF-1 activity, is controlled by oxygen tension.

Since HIF-1 α gene is precarious for oral wound management subsequent extraction of teeth, and meanwhile it has a great genetic diversity, mutual SNPs in HIF-1 α could have a role in the entrance of harshly resorbed mandibular ridges. SNP 1772C>T is one of the two common HIF-1 α mutations (1772C>T and 1790G>A). It is a coding SNP located in the ODD domain of exon 12 in HIF-1 α gene leading to an amino acid change from proline 582 to serine. This SNP has been extensively studied trying to discover its correlation with various types of cancer, ischemic heart disease, osteonecrosis, chronic obstructive pulmonary disease, and diabetes and even to find out a genetic etiology for the high performance of elite athletes in power-oriented sports. Individuals experience RRR at varying rates as a result of wound healing following tooth extraction. Relative hypoxia is an important trigger for proper wound healing. HIF-1 is protected from degradation in hypoxic circumstances and triggers a sequence of genes that allow cells to adapt to hypoxia. As a consequence, coding SNPs in the HIF-1 gene might affect the responsiveness of diverse cells to hypoxia, resulting in a different wound healing phase following tooth extraction. This could lead to an exaggerated pattern of RRR. An SNP at 1790G>A (rs11549467) can be used as a marker to predict the prognosis of the alveolar ridge after extraction of teeth, according to Paek *et al.*, [15]. Therefore, a treatment strategy can be established appropriately, declining excessive expenditures. An Egyptian study identified 1772C>T (rs11549465) as a marker predicting the future condition of the residual alveolar ridge [16].

Conclusion

Disease-induced bone loss, dental decay, and defects are becoming a worldwide concern with a high incidence, negatively impacting the fitness and advantage of life of the entire population. In many cases, it's better to intervene in the disease rather than remove its cause from the gene. It is important that dentists recognize the clinical characteristics of these rare conditions early on since they are the first people to identify them. HIF-1 functions, target genes, and activation pathways are being better understood, enabling the development of novel treatments for diseases like

residual ridge resorption. In spite of the gray areas in the understanding of HIF-1, it remains a highly priority target for drug development. There is promising evidence that modulating the HIF-1 pathway could have a significant impact on treatment, impacting millions of people who suffer from such diseases.

References

- [1]. Avila G, Galindo-Moreno P, Soehren S, Misch CE, Morelli T, Wang HL. A novel decision-making process for tooth retention or extraction. *J Periodontol*. 2009 Mar;80(3):476-91. Pubmed PMID: 19254132.
- [2]. Chen SC, Chueh LH, Hsiao CK, Wu HP, Chiang CP. First untoward events and reasons for tooth extraction after nonsurgical endodontic treatment in Taiwan. *J Endod*. 2008 Jun;34(6):671-4. Pubmed PMID: 18498886.
- [3]. Klemetti E. A review of residual ridge resorption and bone density. *J Prosthet Dent*. 1996 May;75(5):512-4. Pubmed PMID: 8709016.
- [4]. Baxter JC. Relationship of osteoporosis to excessive residual ridge resorption. *J Prosthet Dent*. 1981 Aug;46(2):123-5. Pubmed PMID: 7024523.
- [5]. Xie Q, Ainamo A, Tilvis R. Association of residual ridge resorption with systemic factors in home-living elderly subjects. *Acta Odontol Scand*. 1997 Oct;55(5):299-305. Pubmed PMID: 9370028.
- [6]. Bacon NC, Wappner P, O'Rourke JF, Bartlett SM, Shilo B, Pugh CW, Ratcliffe PJ. Regulation of the Drosophila bHLH-PAS protein Sima by hypoxia: functional evidence for homology with mammalian HIF-1 alpha. *Biochem Biophys Res Commun*. 1998 Aug 28;249(3):811-6. Pubmed PMID: 9731218.
- [7]. Jahangiri L, Devlin H, Ting K, Nishimura I. Current perspectives in residual ridge remodeling and its clinical implications: a review. *J Prosthet Dent*. 1998 Aug;80(2):224-37. Pubmed PMID: 9710828.
- [8]. Shanbhag S, Karnik P, Shirke P, Shanbhag V. Cone-beam computed tomographic analysis of sinus membrane thickness, ostium patency, and residual ridge heights in the posterior maxilla: implications for sinus floor elevation. *Clin Oral Implants Res*. 2014 Jun;25(6):755-60. Pubmed PMID: 23560797.
- [9]. Kreisler M, Behneke N, Behneke A, d'Hoedt B. Residual ridge resorption in the edentulous maxilla in patients with implant-supported mandibular overdentures: an 8-year retrospective study. *Int J Prosthodont*. 2003 May-Jun;16(3):295-300. Pubmed PMID: 12854795.
- [10]. Ardakani FE, Azam AR. Radiological findings in panoramic radiographs of Iranian edentulous patients. *Oral Radiology*. 2007 Jun;23(1):1-5.
- [11]. Kim JH, Oh MY, Paek J, Lee J. Association between FGFR1OP2/wit3.0 polymorphisms and residual ridge resorption of mandible in Korean population. *PLoS One*. 2012;7(8):e42734. Pubmed PMID: 22880093.
- [12]. Sundar SS, Jayesh SR, Hussain S. Association of matrix metalloproteinase 1 gene promoter mutation and residual ridge resorption in edentulous patients of South Indian origin. *J Pharm Bioallied Sci*. 2015 Aug;7(Suppl 2):S652-5. Pubmed PMID: 26538937.
- [13]. Song JH, Lee JH. Single nucleotide polymorphisms and haplotypes in vascular endothelial growth factor gene and residual ridge resorption of mandible in Korean population.
- [14]. Alzain S, Al Sheikh H, Al Thomali A, Al-Mukaynizi F, Almoberk N, Al-malki SA, Parine NR, Warsy A. Significant association of a single nucleotide polymorphism in the upstream region of FGFR1OP2/wit3. 0 gene with residual ridge resorption of mandible in Saudis. *Biocell*. 2020;44(1):55.
- [15]. Paek J, Oh Y, Kim J, Lee JH. Single nucleotide polymorphisms in HIF-1α gene and residual ridge resorption (RRR) of mandible in Korean population. *Gene Expr*. 2015;16(3):137-44. PMID: 25700369.
- [16]. Emam SM, Amin AK, Issa NM, El-Attar MS. A Genetic Association Study of a Specific Gene and Severe Form of Resorption in the Edentulous Mandible in the Egyptian Population. *J Prosthodont*. 2019 Apr;28(4):409-415. Pubmed PMID: 30829443.