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Role of genetic polymorphisms in residual ridge resorption of mandible – A scoping review☆

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ABSTRACT

Residual ridge (RR) refers to the clinical alveolar ridge that remains after the bone and soft tissues have healed following tooth extraction. This ridge undergoes resorption, which is most rapid during the first six months of post-extraction. Subsequently, bone resorption continues at a slower pace throughout life, leading to significant loss of jaw structure over time. This process is commonly known as residual ridge resorption (RRR). RRR is a major factor contributing to the loss of stability and retention, especially in mandibular complete dentures. Severe resorption of the maxillary and mandibular ridges can also lead to a sunken cheek appearance, poorly fitting and unstable dentures, and associated pain and discomfort. Though the etiology of residual ridge resorption remains unclear. It is believed that certain cytokines and individual genetic variations may influence the RRR process. Thus, reviewing the studies that discuss genetic association with the health and resorption of alveolar bone may give clear view on the etiology, help to define the risk and strategize preventive and personalized management of the disease. Hence, we undertook a scoping review to understand the potential genetic factors influencing the Residual ridge resorption (RRR). This review employed PRISMA-ScR extension protocols for scoping review. The results of the study provided significant association between genetic polymorphisms, especially of single gene nucleotide polymorphisms with mandibular residual ridge resorption. Hence understanding the genetic predisposition of patients can guide the clinicians in identifying patients at higher risk of RRR, enabling preventive measures, proactive intervention and careful designing of the prothesis.

1. Introduction

Bone resorption is a chronic, progressive and irreversible process that occurs in all patients following the tooth loss [1]. Despite the most recent advancements in dentistry, the loss of natural teeth is inevitable. However, with loss of teeth, the loss of alveolar bone is a definite consequence which cannot be controlled. It is impossible to predict the amount of bone loss and prevent resorption as ridge resorption is a continuous process [2]. The residual ridge can be defined as the shape of the clinical alveolar ridge after healing of soft tissues and bone after extraction of teeth [3].

Edentulism has been regarded as a physiological manifestation of an aging process. However, in Prosthodontics it is classified as a pathology. Residual ridge resorption (RRR) was described by Atwood as "Major Oral Disease Entity". It was described as bone loss that commences with the extraction of teeth and continues even after prosthodontic rehabilitation. Residual ridge resorption is the most common problem seen in elderly patients. Patients with resorbed ridges pose extremely challenging situations for prosthodontic rehabilitation, as the existing basal bone foundation is compromised for support and retention for the denture [3,4].

It is established that RRR is multifactorial in origin, numerous factors, including prostaglandins, osteoclast activating factor, dental plaque endotoxins, physical activity, heredity, and factors influencing gene expression of specific proteins, have been linked to the pathophysiology of RRR. Other factors for bone loss related to age includes the race, diet, decreased estrogen secretion, and factors affecting physical activity [5]. Genetics provides relevant solutions to chronic conditions which can be

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diagnosed, prevented, and treated even before they manifest. RRR, being a chronic pathology, also has a genetic association [4,6].

The residual ridge formed after the healing of extraction socket, involves a series of events beginning with clot formation, capillary ingrowth into the extraction socket, appearance of osteoblastic cells, reappearance of hematopoietic tissue and lastly bone resorption by osteoclasts. As the edentulous residual ridge is formed from wound healing process, literature suggests that the single nucleotide polymorphisms (SNPs) in genes that are responsible for the healing of mucosal and bone tissue can be contributing factors that lead to abnormal ridge formation or affect its maintenance [7]. Thus, SNP in the genes associated with the physiological events following extraction can induce enhanced RRR. The hypoxia inducible factor −1 α (HIF-1 α) gene plays a crucial role in the healing of oral wounds following tooth extraction. Common SNPs in HIF-1α may contribute to the RRR because of its high genetic variability [8]. SNPs in various negative regulators of bone resorption such as tumour necrosis factor receptor superfamily member 11 A (TNFRSF11A) and tumour necrosis factor receptor superfamily member 11B (TNFRSF11B) can also induce RRR [5]. These studies have revealed strong correlations between genetic polymorphisms and RRR. Thus, SNP typing can be a great aid for genetic analysis. In addition, to revealing the causes, long-term prognosis, rate of ridge resorption and morphologies, it can expedite the identification and localization of genes contributing to the severe RRR. Furthermore, SNP mapping can make it easier to apply newer and advanced therapeutic techniques to present the resorption and strategies to enhance the vertical bone in edentulous ridges [9–11]. Although various studies [5,9–11]. have established the role of various genetic polymorphisms in RRR, no comprehensive review has explored the full spectrum of genetic SNPs involved in the condition. This gap in literature prompted the initiation of a scoping review, aiming to synthesize existing research on the genetic influences of RRR, with a particular focus on SNPs. By mapping these genetic factors, the review seeks to identify research gaps and offer insights for future studies and clinical applications in Prosthodontics.

2. Methodology

2.1. Study design

The present review follows PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [12] extension for scoping reviews for identifying the research question, selecting the appropriate studies, determining inclusion and exclusion criteria, extraction of data, and summarizing the results.

2.2. Literature search

A literature search of articles published until February 2024, was performed in three databases including PubMed, Web of Science and Scopus using the refined search strategy developed after identifying the relevant keywords for the research question with an accordant Boolean operator. The search strategy used in all three databases is mentioned in detail in Table 1. Manual searches were conducted in addition to database searches. Records available as titles and abstracts in English with the relevant databases were considered for further scrutiny. Articles from the reference lists deemed most relevant were examined to increase the scope of the search. Both in vivo and in vitro studies were included. Fig. 1 shows the distribution of the articles searched. The final search results were exported to Mendeley Desktop v. 1.19.8 (Mendeley Ltd., Elsevier, Netherlands) and duplicates were removed before proceeding with further phases of study inclusion in the review by scanning relevant and eligible studies.

2.3. Eligibility criteria

Two independent reviewers (S.B.V and S.S.S) screened the full-text articles corresponding to the selected abstracts. Any disagreements or uncertainties were resolved through a mutual consensus process and the included articles were categorized according to the genetic polymorphism investigated. The inclusion and exclusion criteria are listed in Table 2.

Table 1
Search strategy used in various databases.

Databases	Search terms
Pubmed	((("ridge"[All Fields] OR "ridge s"[All Fields] OR "ridged"[All Fields] OR "ridges"[All Fields] OR "ridging"[All Fields]) AND ("resorption"[All Fields] OR "resorptional"[All Fields] OR "resorptions"[All Fields] OR "resorptive"[All Fields] OR "resorptives"[All Fields])) OR (("residual"[All Fields] OR "residuals"[All Fields]) AND ("ridge"[All Fields] OR "ridge s"[All Fields] OR "ridged"[All Fields] OR "ridges"[All Fields] OR "ridging"[All Fields]) AND ("resorption"[All Fields] OR "resorptional"[All Fields] OR "resorptions"[All Fields] OR "resorptive"[All Fields] OR "resorptives"[All Fields])) OR (("edentulate"[All Fields] OR "edentulation"[All Fields] OR "edentulism"[All Fields] OR "edentulousness"[All Fields] OR "mouth, edentulous"[MeSH Terms] OR ("mouth"[All Fields] AND "edentulous"[All Fields]) OR "edentulous mouth"[All Fields] OR "edentulous"[All Fields]) AND ("mandible"[MeSH Terms] OR "mandible"[All Fields] OR "mandibles"[All Fields] OR "mandible s"[All Fields])) OR (("mandible"[MeSH Terms] OR "mandible"[All Fields] OR "mandibular"[All Fields] OR "mandibulars"[All Fields]) AND ("atrophie"[All Fields] OR "atrophy"[MeSH Terms] OR "atrophy"[All Fields] OR "atrophied"[All Fields] OR "atrophies"[All Fields] OR "atrophying"[All Fields])) OR ("bone resorption"[MeSH Terms] OR ("bone"[All Fields] AND "resorption"[All Fields]) OR "bone resorption"[All Fields])) AND ("genetic"[All Fields] OR "genetical"[All Fields] OR "genetically"[All Fields] OR "genetics"[MeSH Subheading] OR "genetics"[All Fields] OR "genetics"[MeSH Terms]) AND (("genetic"[All Fields] OR "genetical"[All Fields] OR "genetically"[All Fields] OR "genetics"[MeSH Subheading] OR "genetics"[All Fields] OR "genetics"[MeSH Terms]) AND ("factor"[All Fields] OR "factor s"[All Fields] OR "factors"[All Fields])) AND ("polymorphic"[All Fields] OR "polymorphics"[All Fields] OR "polymorphism s"[All Fields] OR "polymorphism, genetic"[MeSH Terms] OR ("polymorphism"[All Fields] AND "genetic"[All Fields]) OR "genetic polymorphism"[All Fields] OR "polymorphism"[All Fields] OR "polymorphisms"[All Fields]) AND ("genetic"[All Fields] OR "genetical"[All Fields] OR "genetically"[All Fields] OR "genetics"[MeSH Subheading] OR "genetics"[All Fields] OR "genetics"[MeSH Terms]) AND ("polymorphism, single nucleotide"[MeSH Terms] OR ("polymorphism"[All Fields] AND "single"[All Fields] AND "nucleotide"[All Fields]) OR "single nucleotide polymorphism"[All Fields] OR ("single"[All Fields] AND "nucleotide"[All Fields] AND "polymorphisms"[All Fields]) OR "single nucleotide polymorphisms"[All Fields])
Scopus	((TITLE-ABS-KEY (residual AND ridge AND resorption) OR TITLE-ABS-KEY (ridge AND resorption) OR TITLE-ABS-KEY (edentulous AND mandible) AND TITLE-ABS-KEY (mandibular AND atrophy) OR TITLE-ABS-KEY (bone AND resorption))) AND ((TITLE-ABS-KEY (genetics) AND TITLE-ABS-KEY (genetic AND factors) AND TITLE-ABS-KEY (single AND nucleotide AND polymorphisms)))
Web of science	ridge resorption (All Fields) OR residual ridge resorption (All Fields) OR edentulous mandible (All Fields) OR mandibular atrophy (All Fields) OR bone resorption (All Fields) AND genetics (All Fields) AND genetic factors (All Fields) AND polymorphisms (All Fields) AND single nucleotide polymorphisms (All Fields)

2.4. Data extraction and synthesis

For the scoping review the authors classified the manuscripts based on the SNPs or genetic polymorphism studied in relation to ridge resorption. The data was entered on an MS Excel 2019 sheet, which included the following: authors, year of publication, type of study, population studied, age of the patient, type of genetic polymorphism, height of the remaining alveolar bone in the mandible (Table 3).

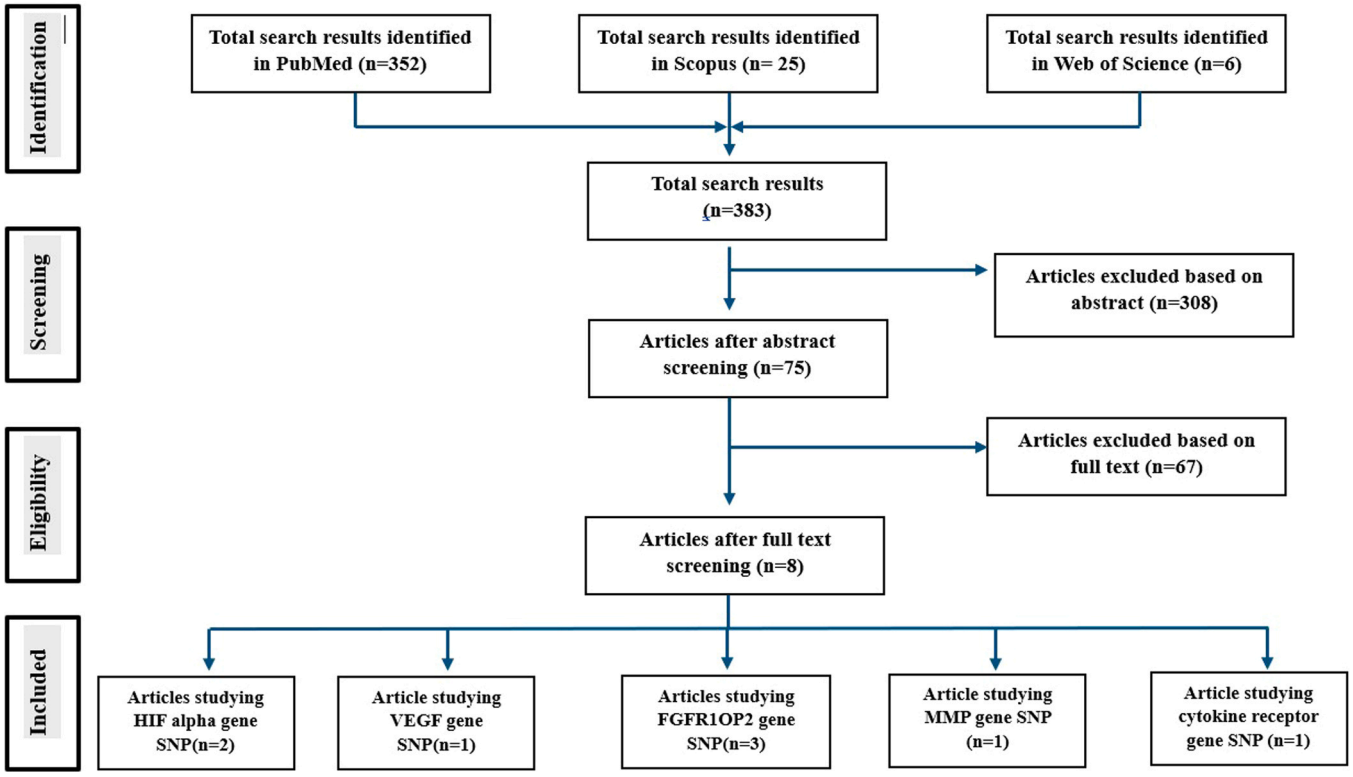

Fig. 1. PRISMA flowchart illustrates the search and study selection process.

Table 2
Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion criteria
1. Interventional studies, case control studies and observational studies which investigated the relationship between genetic polymorphisms/SNP and mandibular residual ridge resorption were included.	1.Studies with patients of RRR but without exclusion of systemic conditions.
2. Studies with patients showing RRR but free from any systemic conditions.	2.Studies with patients having history of bone augmentation or bone transplantation.
3. Studies involving participants who were completely edentulous or partially edentulous were included.	3.Abstracts of works authored and published in languages other than English. 4. Systematic reviews, narrative reviews, or systematic and meta-analysis.

2.5. Quality assessment

The quality assessment of the selected articles was done using NIH quality assessment tool [13] as shown in Tables 4 and 5. This 14-item checklist has proven to be a reliable and useful tool for observational cohort and cross-sectional studies and case control studies. Each question had five options – Yes/No/Cannot Determine/ Not Applicable/ Not Reported. For cross sectional studies Scores of 0–4 was considered poor, 5–9 was considered fair, and scores of 10–14 were considered good quality. For case control studies, scores of 0–4 (poor), 5–8 (fair), and 9–12 (good) were considered to assess the quality of the included studies. The quality assessments were independently conducted by two authors (S.B.V and S.S.S). Any discrepancies were resolved through discussion and consensus.

The collected data was evaluated for eligibility for the meta-analysis. However, meta-analysis could not be performed due to the substantial variations in the genetic polymorphisms studied among the included studies.

3. Results

A total of 383 articles were obtained after a literature search of three databases electronically and manually. 352 articles were identified in PubMed/MEDLINE, 25 in Scopus, 6 in Web of Science. Further, Screening for relevant articles based on title and abstract was done. A total of 308 articles were non-relevant, so were excluded. Further 75 full text articles were reviewed according to eligibility criteria and based on exclusion criteria 67 were removed. Eight full text reports were finally quantitatively summarized. The PRISMA flowchart in Fig. 1 illustrates the entire process. Studies ranged in publication date from 2011 to 2020.

3.1. Types of study

AlSheikh et al. [5], Kim et al. [14] and Alzain et al. [15] conducted case control studies, Song et al. [16], Sunder et al. [17] Paek et al. [8] and Suwanwela et al [18] conducted cross sectional studies and Emam et al. [19] conducted case control retrospective study.

3.2. Participants

Three studies from Korea included a total of 356 patients to study the role of various SNPs in residual ridge resorption [8,15,16]. Two studies were conducted in Saudi Arabia analyzing a total of 384 patients for different SNPs [5,17]. Studies conducted by AlSheikh et al. [5], Paek et al. [8], Emam et al. [19], Alzain et al. [15], Kim et al. [14] and Song et al. [16] analyzed both completely edentulous and partially edentulous patients.

3.3. Age and condition

The age ranged from 40 to 71 years. Participants were completely

Table 3
The studies showing the association of genetic factors with residual ridge resorption (RRR).

Author name /year	Type of study	Study place	Avg age	Patient Condition	Sample collection	Mean bone height	SNP genotypes studied	Result (association of genetic factors on RRR)
AlSheikh et al. 2020 [5]	Case control	Saudi Arabia	50 yrs	Completely and partially edentulous patients	Saliva	13 mm	SNPs, including TNF-a (rs1800629), IL10 (rs1800872, rs1800896), IL1RN (rs419598), TNFRSF11B (rs11573847), TNFRSF11A (rs4485469), NOD2 (rs5743289), and MMP1 (rs1799750, rs554499, rs5854)	1. rs1800896 (1082 T > C) in the promoter region of the gene and a transversion mutation are significantly associated with RRR 2. Wild-type allele T was >four times predisposed to RRR compared to the mutant C allele
Paek et al. 2013 [8]	Cross sectional	Korea	70 yrs	Completely and partially edentulous patients for atleast 2 years	Saliva	15.17 mm	SNP of the HIF−1a gene, and the residual ridge resorption (RRR)	minor allele of rs11549467 was associated with the RRR
Emam et al. 2019 [19]	Case control retrospective study	Egypt	40–70 yrs	Completely edentulous patients	Saliva	11.5 mm in study group Type 3 residual ridge	SNP 1772 C>T in HIF−1α gene and the etiology of residual ridge resorption	Significant association between the TT genotype of SNP 1772 C>T in HIF−1α gene and the presence of severely resorbed edentulous mandibular ridge
Alzain et al. 2020 [15]	Case control	Saudi arabia	49 yrs	Completely/ partially edentulous patients	Saliva	13 mm	SNPs in fibroblast growth factor receptor 1 oncogene partner 2 (FGFR1OP2) in RRR	SNP rs2279351 associated significantly with RRR, and the mutant C allele was highly predisposed.
Kim et al. 2012 [14]	Case Control	Korea	70 yrs	Completely and partially edentulous patients for atleast 2 years	Saliva	Type II (18.0661.69 mm); 24 as Type III (12.7261.21 mm); and 11 as Type IV (9.7560.65 mm)	polymorphisms in FGFR1OP2 and its relation with residual ridge resorption of mandible	minor allele of ss518063493 may be associated with excessive atrophy of edentulous mandible
Suwanwela et al. 2011 [18]	Cross sectional	USA	61 yrs	Completely edentulous patients for more than 10 years	Gingiva	Type II (18.061.7 mm); Type III (12.661.4 mm); Type IV (8.361.5 mm).	SNPs of FGFR1OP2/wit3.0 and excessive atrophy of edentulous mandible.	Minor allele of rs840869 or rs859024 were associated with excessive atrophy of edentulous mandible.
Sundar et al. 2015 [17]	Cross sectional	India	60 yrs	Completely edentulous patients	Buccal cells	23 mm for class I, 18.7 mm for class II, and 12.8 mm for class III	SNP of MMP−1 and continuous atrophy of edentulous mandible	patients with the alveolar bone resorption exhibited more of 2 G allele while only 21.2 % of them showed 1 G allele
Song et al. 2014 [16]	Cross sectional	Korea	71 yrs	Completely/ partially edentulous patients for atleast 2 years	Saliva	15 mm	SNP of VEGF gene i.e rs1570360 in chr6:43737830, rs25648 in chr6:43738977, rs3025039 in chr6:43752536 and RRR	haplotype A-C-C from the second prevalent type containing the 2nd and the 3rd LD block, showed association with RRR

edentulous or partially edentulous for at least a period of 2 years [8,12, 16] and in one study more than 10 years [18].

3.4. Quality assessment of included studies

The NIH quality assessment tool was used to assess the quality of the 8 included studies (Tables 3 and 4). Since the scores of the case-control studies ranged between 5–8, the studies were classified as fair quality, and all the cross-sectional studies scores ranged between 5 and 9, thus these studies were also classified as fair quality.

3.5. Height of the mandibular residual ridge

Mandibular residual height was measured clinically and radiographically using digital panoramic radiograph. The bone height is the measure of the distance between superior and inferior borders of the mandible. American College of Prosthodontists (ACP) classified the bone height into Type 1; bone height of residual mandibular ridge is 21 mm or greater, Type II; bone height of residual mandibular ridge is 16–20 mm, Type III; bone height of mandibular residual ridge is 11–15 mm or Type IV; bone height of mandibular residual ridge is 10 mm or less. Type III and Type IV were considered as severely resorbed mandibular ridges [20]. In the study done by Kim et al. the mean mandibular bone height was 18.9 mm, 24 patients had Type III ridge (13 mm) and 10 patients had type IV ridge (10 mm) [14]. The mean mandibular bone height was 15.17 mm and varied from 8.52 mm to 35.08 mm in the study done by Paek et al. [8]. In the study by Al Zain et al. the bone height showed a marked variation in the edentulous and partially edentulous patients and ranged from 13 to 34.6 mm [15]. Sunder et al. in his study observed that mean bone height was 18.7 mm for class II, and 12.8 mm for class III patients [17]. In the study done by Emam et al. the range of the mandibular height in the study group was 8–15 mm, and mean height was 11 mm [19].

3.6. Samples for genomic deoxy ribose nucleic acid (DNA) extraction

The DNA extraction for genomic analysis was done in six studies [5, 8,12,15,16,19] using saliva samples, buccal cells were used in one study

Table 4
Quality assessment of the included case control studies.

Quality assessment	AlSheikh et al. 2020 [5]	Emam et al. 2019 [19]	Alzain et al. 2020 [15]	Kim et al. 2012 [14]
1.Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and define	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50 %?	Not reported	Not reported	Not reported	Not reported
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	No	Yes	No	No
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured	No	No	No	No
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	NA	NA	NA	NA
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	No	No	No	No
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	NA	NA	NA	NA
13. Was loss to follow-up after baseline 20 % or less?	NA	NA	NA	NA
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	Yes	Yes	Yes
Summary quality	Fair (7)	Fair (8)	Fair (7)	Fair (7)

[17] and in one study gingival biopsy was taken from the patients for DNA extraction.

3.7. Association of SNPs with residual ridge resorption

Studies investigated the role of presence of various SNP in severely resorbed mandibular edentulous ridge are summarized in Table 1. Paek et al. [8] and Emam et al. [19] studies investigated the role of HIF-1α gene SNP in RRR. Emam et al. [19] observed that TT genotype of the 1772 C>T polymorphism of HIF1-α gene to be associated with residual ridges that exhibited severe atrophy. Paek et al. [8] found SNP rs11549467 (A588T) in HIF-1α gene to be linked with the RRR in Korean population.

Song et al. [16] analyzed the role of vascular endothelial growth factor (VEGF) gene SNP in ridge resorption and found the VEGF variant rs1570360 having association with mandibular ridge resorption in Korean participants.

Role of genotype of fibroblast growth factor receptor 1 oncogene partner 2/ wound inducible transcript 3.0 (FGFR1OP2/wit3.0) SNP in residual ridge resorption was evaluated by three studies. Suwanwela et al. [18] investigated the potential correlation between FGFR1OP2/-wit 3.0 gene SNPs and residual crest resorption. Six SNPs studied were studied rs2279351, rs840869, rs859024, rs2046937, rs1051513 and rs2129091. A correlation was found between SNPs rs840869 and rs859024 with atrophy of mandible [18]. Kim et al. [14] studied eight SNPs (rs2279351, rs2306852, rs78054962, rs840869, ss518063498, ss518063493, ss518063913, ss518063476) that were not in high linkage disequilibrium at r2 threshold of 0.80 in the of fibroblast growth factor receptor 1 oncogene partner 2 (FGFR1OP2) gene. The results did not show significant correlation between SNPs in FGFR1OP2 gene and RRR. Only one participant showed positive association of the dominant minor allele of ss518063493 with resorptive changes in residual ridge [14]. Alzain et al. [15] investigated the role of SNPs of the FGFR1OP2 gene in the development of RRR in Saudi individuals. SNPs rs2279351, rs78054962 and rs2306852, present in the FGFR1OP2 gene promoter region were studied, with only SNP rs2279351 showing association with RCR.

Sunder et al. [17] evaluated the relation of SNP of Matrix metalloproteinase-1 (MMP-1) and mandibular ridge atrophy and observed found 22 % of the experimental RRR group with MMP-1 gene 1 G polymorphism and 78 % of the group with 2 G polymorphism. AlSheikh et al. [5] analyzed Saudi patients who were completely or partially edentulous for cytokine receptor gene SNP. The TNFRSF11B (rs11573847), TNFRSF11A (rs4485469), Nucleotide-binding oligomerization domain-2 (NOD2) (rs5743289), MMP1 (rs1799750, rs554499, rs5854), Interleukin (IL)10 (rs1800872, rs1800896), IL1RN (r19598), and TNFα (rs1800629) were among the SNPs that were genotyped. He observed transversion mutation and rs1800896 (-1082T>C) in the IL10 gene promoter region have association with RRR.

Table 5
Quality assessment of the included cross-sectional studies.

Quality assessment	Paek et al. 2013 [8]	Suwanwela et al. 2011 [18]	Sundar et al. 2015 [17]	Song et al. 2014 [16]
1.Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and define	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50 %?	Not reported	Not reported	Not reported	Not reported
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	No	No	No	No
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured	No	No	No	No
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	No	No	No	No
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	NA	NA	NA	NA
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	No	No	No	No
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	NA	NA	NA	NA
13. Was loss to follow-up after baseline 20 % or less?	NA	NA	NA	NA
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	Yes	Yes	Yes
Summary quality	Fair (6)	Fair (6)	Fair (6)	Fair (6)

4. Discussion

With advancing years and longer life spans, edentulism has becomes more prevalent. This presents a prosthodontic challenge, as older patients with dentures place greater demands on dentists. The treatment for these patients depends upon the degree of RRR observed [17]. As the residual ridge is predominantly made up of distinct soft tissue and the alveolar bone formed after tooth extraction, any defects in socket matrix formation or cellular activity will lead to delayed healing. The residual ridge undergoes resorption, which is most rapid during the first six months of post-extraction. Subsequently, bone resorption continues at a slower pace throughout life, leading to significant loss of jaw structure over time [14]. The degree of RRR varies among individuals and populations, and its causes and variability remain incompletely understood. However, significant variations in bone response have been observed even when the above factors are controlled. It is possible that genetic differences between individuals influence their RRR [3]. RRR may be caused due to the genetic regulatory mechanisms that alter the gene expression thereby changing the quantity and quality of bone formed [19].

4.1. Role of genetic polymorphism in promoting residual ridge resorption

4.1.1. Hypoxia inducible factor-1(HIF-1)

Following tooth extraction, the blood vessels in the extraction socket are damaged, cutting off blood supply and reducing the surrounding oxygen pressure, causing tissue to become hypoxic. HIF-1 is a transcriptional complex crucial for maintaining systemic and cellular oxygen homeostasis. It acts as the primary controller of oxygen-dependent genes, with 60 known target genes under its regulation [8,16]. HIF-1 promotes vascularization in hypoxic areas and extracellular matrix metabolism. These processes are extremely important for the healing of wounds after teeth extraction [8,15,16]. HIF-1 consists of α and β subunits. The alpha subunit, which controls HIF-1 activity, is in turn controlled by oxygen tension. In hypoxic situations, HIF-1α expression persists until tissues achieve a balance of oxygen supply and consumption [21]. It is upregulated in hypoxia and serves as a crucial factor for angiogenesis during osteogenesis. The activation of HIF-1α is a specific and sensitive response to hypoxia, which induces the expression of various pro-angiogenic factors, such as angiotensin-2, VEGF, heme oxygenase-1, and inducible nitric oxidase. In addition, HIF-1α has the capacity to augment osteoblast proliferation, enhance their resilience to hypoxic and ischemic environments, and promote angiogenesis in hypoxic tissues [22]. Since HIF-1α gene has an important role in wound healing after extraction of tooth, and due to its high genetic diversity, SNPs in HIF-1α can result in severely resorbed mandibular ridges [19].

Among the two HIF-1α mutations 1772 C>T and 1790 G>A, most seen is SNP 1772 C>T. This SNP results due to a change of amino acid proline 582 to serine in the HIF-1 gene's ODD domain of exon 12. Success of wound healing largely depends on relative hypoxia. In hypoxia, degradation of HIF-1 is protected, and a series of genes are activated to help the cells to adjust to low oxygen levels. Coding SNPs in the HIF-1 gene may therefore alter the hypoxia responsiveness of different cells, leading to a distinct wound healing phase following tooth extraction. This could lead to an accentuated RRR pattern [18,19]. Further, Paek et al. [8] reported SNP rs11549467 (A588T) in HIF-1α gene to be associated with the RRR, through its significant role in altering the bone remodeling balance resulting in RRR. Further, Emam et al. [19] observed that TT genotype of the 1772 C>T polymorphism of HIF1-α gene is associated with the presence of severely atrophied residual ridges in completely edentulous Egyptians.

4.1.2. Vascular endothelial growth factor (VEGF)

Due to the constant mechanical load from the periodontal ligament that connects the teeth, the healing process following tooth extraction leaves the edentulous jaw with a saddle-shaped residual ridge that eventually disappears; Thus, it is believed that this alteration is connected to the ongoing pattern of alveolar bone resorption. The reduction in the partial pressure of oxygen is the most noticeable event from the reduced mechanical load. The HIF-1-regulated VGEF has been closely associated to angiogenesis and bone turnover, both of which are conditions where partial oxygen pressure changes [16]. VEGF is one of the target genes of bone remodeling and is implicated in angiogenesis among the genes that HIF-1 expresses to regulate osteoclastic bone resorption and bone remodeling. It has been observed that upregulation of VEGF occurs when HIF-1 expression is increased [23]. Additionally, VEGF plays a critical role in osteoclastic bone resorption and is essential for appropriate bone remodeling. The formation of a new endothelial vessel is indicated by VEGF expression, is a necessary stage in the bone deposition process where osteoclasts resorb bone [24].

Song et al. [16] demonstrated a statistically significant correlation of mandibular RRR with SNP rs1570360 in the dominant group and haplotype A-C-C. The haplotype typically provides stronger evidence of association than individual SNP genotypes. Given the cell-type and stimulus specificity of the genotype effect on VEGF expression, it appears to be a highly adaptive process from a physiological standpoint. This is particularly evident as the residual ridge transitions from its original function of supporting the tooth to the process of atrophy [16].

4.1.3. FGFR1 oncogene partner 2 (FGFR1OP2)

The trabecular bone of edentulous jawbone undergoes remodeling after tooth extraction at a proportional rate with other bones, but a noticeable osteoclastic activity is restricted along the external surface of the residual ridge interfacing the oral mucosa. Therefore, the edentulous oral mucosa may have an impact on the residual ridge atrophy. The gingival margins shrink toward the center of the extraction socket during the initial stages of wound healing following dental extractions, and the epithelium quickly reintegrates [25].

The FGFR1OP2 gene is one of the important factors involved in the wound healing process occurring in the oral cavity. It is observed that the SNP in this gene is associated with severe atrophy of edentulous jaw. In the early healing period, the extraction socket involves the proliferation of oral fibroblasts which upregulates the expression of FGFR1OP2/wit3.0 [8,10].

FGFR1OP2/wit3.0 is a cytoskeleton molecule which polymerizes and positions along the collagen fibers that align along areas of stresses in bone. It has been postulated that an increase in this molecule accelerates the contraction of the collagen gel populated with fibroblast cells. Further heterozygous null mutation of FGFR1OP2/wit3.0 slows down the mobility rate of fibroblastic cells. It has been postulated that this molecule could potentially regulate the increased contraction of oral cavity wounds [25].

Suwanwela et al. [18] showed that the degree of mandibular atrophy following the tooth extraction can be predicted by the genotype of the FGFR1OP2/wit3.0 alleles. Specifically, they found a potential correlation between the SNPs rs840869 and rs859024 and severe atrophy of mandible. Individuals with rs840869 and/or rs859024 SNPs belonged to the ACP type III/IV group which is the group with vertical height of the edentulous mandible lower than 15 mm measured following the protocol of the ACP. The SNPs in FGFR1OP2/wit3.0 hide the normal wound contraction thereby promoting the ridge resorption [17]. A study by Kim et al. [14] did not show any correlation between SNPs in FGFR1OP2 gene and atrophic changes of residual ridges. Only one participant showed correlation of dominant minor allele of ss518063493 with excessive atrophic changes in residual ridge. Although this result cannot be proven statistically, it can be predicted that patients carrying the ss518063493 dominant minor allele, have an extreme risk of edentulous lower ridge atrophy [14]. Alzain et al. [15] reported an important association between the presence of SNP rs2279351 in FGFR1OP2 gene to residual crest resorption (RCR). The development of RCR may be influenced by the FGFR1OP2 gene, which is involved in the process of rapid wound healing in the oral cavity and affects the pace of resorption of the jaw [15].

4.1.4. Matrix metalloproteinase (MMP)

Matrix metalloproteinases, also known as MMPs, are a group of zinc-dependent enzymes found in the extracellular matrix (ECM). They can break down certain proteins that are involved in ECM regeneration. These proteins can break down the structural components of the ECM, such as collagen and gelatin, which enables the ECM to undergo breakdown and regeneration [26]. MMPs are essential for controlling the physiology of the bone. Because bone tissue is dynamic and different types of enzymes are needed to break down the organic component of the bone matrix, MMPs and their inhibitors play a crucial physiological role [26]. Mutations in genes encoding various MMPs can result in severe bone abnormalities [27]. A variety of significant diseases, including osteoarthritis, acute myocardial infarction, rheumatoid arthritis, implant failure, and carcinogenesis, are associated with changes in MMP activity [28].

Sunder et al. [17] found 22 % of the experimental RRR group with MMP-1 gene 1 G polymorphism and 78 % of the group with 2 G polymorphism, however no significant association was found. However, previous studies state that 2 G polymorphism is related with bone loss seen in periodontitis and brings about gene alteration resulting in more destruction of ECM with increased m ribonucleic acid (mRNA) in the inflamed gingival tissue [29]. Also, early implant failures in patients with GG polymorphism of MMP-1 gene at −1607 domain has been related to the osseointegration process [29]. MMP-1 polymorphism can induce higher mRNA levels in inflammatory tissues resulting in increased transcriptional activity causing degradation of major interstitial collagenase responsible for bone loss [30].

4.1.5. Genes encoding the cytokines

Cytokines are peptides and they work as immunomodulating agents. Cytokines are of different kinds ranging from interferons, interleukins (IL), chemokines, lymphokines to tumor necrosis factors (TNF). Tumor necrosis factor-α (TNF-α) is a multifunctional cytokine of TNF ligand superfamily. It regulates various cellular proliferation, differentiation of cells, maintenance of a differentiated phenotype, and cell apoptosis [31,32]. TNF-α affects bone cells in the bone microenvironment in a variety of ways [33]. TNF-α suppresses the synthesis of collagen, DNA, and osteocalcin gene expression in osteoblasts; however, it also promotes the production of proteolytic enzymes like matrix metalloproteinases and plasminogen activators, as well as cytokines like IL-8, IL-6, and monocyte macrophage colony-stimulating factor (MCSF) in these cells [33]. Bone resorption is potently induced by TNF-α. According to reports, TNF-α either directly through activating mature osteoclasts or indirectly through primary effects on osteoblasts, or by promoting the

proliferation and differentiation of precursor osteoclasts, leads to increased bone resorption in vivo and in vitro [33].

A study by AlSheikh et al. [33] observed association between the transversion mutation and rs1800896 (-1082T>C) in the IL10 gene promoter region with RRR. Furthermore, the NOD2 (Nucleotide-binding oligomerization domain-2) gene's rs5743289 also showed a strong correlation with RRR. Thus, it is possible to deduce a relationship between cytokine SNPs and atrophic alterations in residual alveolar ridge.

The results of this scoping review indicate genetic polymorphisms, especially SNPs associated with various genes such as HIF-1α, VEGF, FGFR1OP2, MMP-1 and IL-10 can induce accelerated bone resorption accounting to severe RRR. These findings offer valuable clinical insights, and direction to the clinicians for careful analysis of these genetic variations in patients particularly so that preventive measures and personalized treatment planning can be done. Understanding the genetic predisposition of patients can guide the clinicians in identifying patients at higher risk of RRR, enabling proactive interventions. Patients identified as high-risk can benefit from early preventive strategies, like timely replacement of missing teeth with dental implants to minimize ridge resorption [34]. For edentulous patients with genetic susceptibility, careful design of prostheses to minimize pressure on the alveolar ridge may help reduce further resorption [35]. Implant-supported prostheses may be prioritized to distribute occlusal forces evenly and preserve the residual ridge [36,37]. Advances in tissue engineering and bone regeneration, such as the use of bone grafts or growth factors, could be considered as part of treatment plans for high-risk individuals [38]. Identifying patients with specific SNPs might also enable future genetic or pharmacological interventions targeting the pathways implicated in bone resorption [39].

5. Conclusion and future perspectives

Residual ridge resorption affects the health and quality of life in elderly aged groups. As ridge resorption is a continuous process and has high incidence, prosthodontic rehabilitation is quite challenging. Research on the association of genetic polymorphism of HIF-1α, VEGF, FGFR1OP2, MMP-1 and IL-10 genes with RRR opens new avenues for research, potentially leading to the discovery of novel therapeutic targets for personalized treatment of the condition. Considering genetic screening as part of the diagnostic workflow could help in counseling patients about their predisposition to RRR and tailoring individualized treatment plans. Incorporating these clinical strategies, based on the genetic findings of this study, could pave the way for precision medicine approaches in prosthodontics and oral rehabilitation.

Conflict of interests

The authors declare no conflict of interest related to this article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jdsr.2025.02.002.

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