European Journal of Clinical Pharmacy
Print ISSN: 2385-409X **Online ISSN**: 3105-0409
Website: https://farmclin.com/

Original Research Article

Genetic Polymorphisms and Their Impact on Osseointegration, Peri-Implant Tissue, and Prosthodontic Outcomes

Article History:

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Received: 14-10-2025
Revised: 21-10-2025
Accepted: 05-11-2025
Published: 25-11-2025

Abstract: ***Background:*** Successful dental implant therapy depends on effective osseointegration and stable peri-implant tissue response. While biomechanical factors are well established, emerging evidence suggests that genetic variations influence individual healing and implant outcomes. ***Objectives*** This study evaluated the effect of selected genetic markers on osseointegration, peri-implant tissue response, and prosthodontic outcomes in patients receiving dental implants. ***Methods*** A clinical observational study was conducted on 120 patients receiving 230 dental implants. Implant stability, peri-implant bone levels, soft tissue health, and prosthodontic success were recorded. Genetic analysis identified polymorphisms in genes involved in bone metabolism (COL1A1, BMP2, VDR) and inflammatory regulation (IL-1α, IL-1β, IL-1RN, IL-6, TNF-α, CD14). Associations between genotypes and clinical outcomes were analyzed using multivariate regression models. ***Results*** Patients with favorable osteogenic alleles (COL1A1 GG, VDR CC, BMP2 TT) demonstrated higher implant stability, reduced marginal bone loss, and improved prosthodontic outcomes. Conversely, pro-inflammatory variants (IL-1β TT, TNF-α AA, IL-6 GG, CD14 TT) were associated with increased risk of tissue complications, marginal bone loss, and prosthodontic issues. ***Conclusions*** Genetic variability was significantly associated with variations in osseointegration, peri-implant tissue response, and prosthodontic outcomes within the limitations of this observational study.

Keywords: Dental implants; Osseointegration; Genetic polymorphism; Peri-implant tissue; Prosthodontic outcomes.

INTRODUCTION

Dental implants are the preferred modality for replacing missing teeth due to their high success rates, functional stability, and predictable esthetic outcomes [1,2]. Despite significant advances in surgical techniques, implant surface modifications, and prosthetic materials, variability in clinical outcomes continues to be observed among patients. This inconsistency is increasingly attributed to patient-specific biological factors rather than

procedural shortcomings. Genetic predisposition has emerged as an important determinant of osseointegration, peri-implant tissue health, and long-term prosthodontic success, influencing both early healing and functional stability [3,4]. A deeper understanding of genetic influences allows clinicians to anticipate potential risks, tailor treatment protocols, and improve implant predictability [5,6]. Inflammatory cytokine genes play a pivotal role in peri-implant tissue response. Polymorphisms in interleukin genes, particularly IL-1α, IL-1β, and IL-1RN, have been strongly associated with an increased risk of peri-implant inflammation, marginal bone loss, and peri-implantitis [7,8]. Meta-analyses have demonstrated that carriers of specific IL-1 composite genotypes exhibit a significantly higher susceptibility to peri-implant tissue breakdown compared to non-carriers [9]. Additionally, variants in TNF-α and IL-6 genes have been shown to modulate local inflammatory responses, although their clinical impact appears to be population-specific [10,11,12].

These inflammatory pathways directly regulate osteoclastogenesis and bone resorption, processes that are critical during early implant integration and long-term peri-implant bone maintenance [13]. Genes involved in bone metabolism, including COL1A1, BMP2, and VDR, are essential regulators of osteoblast differentiation, collagen synthesis, and mineralization [14,15,16]. Favorable alleles in these genes have been associated with enhanced osseointegration, improved implant stability, and reduced marginal bone loss, whereas unfavorable variants are linked to delayed bone healing and increased peri-implant tissue complications [17,18,19]. Clinical evidence suggests that such genetic variability may explain differences in implant stability and bone remodeling even when standardized surgical and prosthodontic protocols are employed. Despite the standardization of implant placement techniques and prosthetic rehabilitation protocols, considerable inter-individual variability persists in healing response and implant success. Patients undergoing similar implant procedures may demonstrate divergent outcomes, ranging from predictable osseointegration to early failure or peri-implant disease. This observation underscores the limitations of relying solely on mechanical and prosthetic factors to explain implant success. Host biological responses, particularly genetic regulation of inflammation and bone remodeling, play a crucial role in determining clinical outcomes, emphasizing the need to integrate biological considerations into implant treatment planning [1,3,6,9].

Although numerous studies have investigated individual genetic polymorphisms, there remains a paucity of research integrating genetic, clinical, behavioral, and prosthodontic parameters within a unified analytical framework. Furthermore, population-specific genetic variations may influence the expression and clinical impact of these polymorphisms, particularly in South Asian populations where implant outcome data remain limited. Addressing this gap is essential for developing comprehensive genetic risk profiling strategies that can guide patient selection, prosthodontic design, and maintenance protocols [7,15,17]. In addition to genetic predisposition, patient behavior and oral hygiene practices significantly influence implant outcomes. Studies from Pakistan and comparable regions report that inadequate oral health awareness, plaque accumulation, and poor maintenance behaviors contribute to peri-implant inflammation and tissue breakdown, potentially amplifying the effects of unfavorable genetic profiles [1,6,8]. Emerging evidence also highlights the role of epigenetic regulation and gene–environment interactions in osseointegration and peri-implant tissue response. Environmental factors such as smoking, nutritional deficiencies, and systemic health conditions may modify gene expression and exacerbate inflammatory responses, reinforcing the complex interplay between host genetics and external influences [12,13]. Consequently, integrating genetic insights with clinical evaluation and behavioral assessment represents a critical step toward personalized implant dentistry, optimized prosthodontic planning, and improved long-term patient outcomes [3,9].

Methodology

This observational clinical study was conducted among patients receiving dental implants in maxillary and mandibular sites across prosthodontic clinics in Karachi, Pakistan. A priori sample size calculation was performed using G*Power software (version 3.1) assuming a moderate effect size (f^2 = 0.15), 80% statistical power, alpha level of 0.05, and inclusion of up to 10 predictors in a multivariate regression model. The minimum required sample was calculated as 108 participants; therefore, 120 patients were recruited to compensate for potential attrition and incomplete genetic data. Patients aged 20–65 years with adequate bone volume for implant placement were included. Exclusion criteria comprised uncontrolled diabetes, osteoporosis requiring pharmacologic therapy, chronic corticosteroid use, autoimmune disease, history of head and neck radiotherapy, and active smoking exceeding 10 cigarettes per day. Ethical approval was obtained from the institutional review board, and written informed consent was secured from all participants. Clinical assessment included implant stability measurement using resonance frequency analysis, recorded as Implant Stability Quotient (ISQ) values at placement and at 3, 6, and 12 months. Peri-implant parameters included probing depth, plaque index, bleeding on probing, and

mucosal health status. Standardized digital periapical radiographs were used to measure marginal bone levels with calibrated imaging software.

Prosthodontic outcomes were evaluated through standardized criteria, including restoration fit, retention, occlusal harmony, mechanical complications, and patient-reported satisfaction scores. Examination was performed prior to data collection, and inter-examiner reliability was assessed using Cohen's kappa coefficient ($\kappa > 0.85$ considered acceptable). Genomic DNA was collected using sterile buccal swabs and extracted using standardized commercial kits. Selection of single-nucleotide polymorphisms (SNPs) was based on prior meta-analyses and systematic reviews demonstrating significant associations between specific genetic variants and peri-implant inflammation, bone remodeling, and implant failure risk. Genes involved in bone metabolism (COL1A1, BMP2, VDR) and inflammatory regulation (IL-1α, IL-1β, IL-1RN, IL-6, TNF-α, CD14) were chosen due to their established biological roles in osteoblast differentiation, collagen synthesis, osteoclast activation, cytokine signaling, and host immune response modulation. Genotyping was performed using Polymerase Chain Reaction–Restriction Fragment Length Polymorphism (PCR-RFLP) techniques. A random 10% of samples were re-genotyped to ensure reproducibility, yielding greater than 99% concordance. Genotype and allele frequencies were calculated for each polymorphism. Hardy–Weinberg equilibrium (HWE) was assessed using chi-square goodness-of-fit tests to ensure genetic distribution validity within the study population. Polymorphisms deviating from HWE ($p < 0.05$) were excluded from further multivariate analysis. Descriptive statistics were presented as mean ± standard deviation for continuous variables and frequencies with percentages for categorical variables. Bivariate associations between genetic markers and clinical outcomes were evaluated using independent t-tests, ANOVA, and chi-square tests as appropriate. To determine independent predictors of implant stability and marginal bone loss, multivariate linear regression models were constructed, adjusting for potential confounders including age, sex, implant location (maxilla/mandible), oral hygiene status, and systemic health variables. Adjusted beta coefficients (β) with 95% confidence intervals (CI) were reported for continuous outcomes such as ISQ and bone loss. For binary outcomes, including prosthodontic complications and peri-implantitis, multivariate logistic regression analysis was performed. Adjusted odds ratios (AORs) with 95% confidence intervals were calculated to quantify the strength of association between genetic variants and clinical outcomes. Multicollinearity was evaluated using the variance inflation factor (VIF < 5 considered acceptable). Given the evaluation of multiple genetic polymorphisms across inflammatory and osteogenic pathways, correction for multiple comparisons was performed using the Benjamini–Hochberg False Discovery Rate (FDR) procedure to reduce the risk of type I error. Adjusted p-values < 0.05 after FDR correction were considered statistically significant. Although the sample size (n = 120) satisfied the a priori G*Power calculation for detecting moderate effect sizes ($f^2 = 0.15$, power = 80%, $\alpha = 0.05$), it may be considered modest for extensive multi-gene interaction modeling. Therefore, regression models were constructed using controlled variable entry, and interaction terms were introduced selectively to avoid overfitting. Variance inflation factors confirmed absence of significant multicollinearity.

Environmental and behavioral variables, including smoking status, plaque index, oral hygiene practices, and calcium intake, were recorded through a structured questionnaire. Gene–environment interactions were statistically examined by introducing interaction terms (e.g., IL-1β × smoking status; TNF-α × oral hygiene index) into regression models to evaluate potential modifying effects. Significant interaction effects were interpreted based on interaction coefficients and stratified analyses. A post hoc power analysis confirmed that the final sample size achieved greater than 80% power to detect moderate associations between genetic polymorphisms and primary implant stability outcomes. Statistical analyses were performed using SPSS version 26.0, and a p-value < 0.05 was considered statistically significant.

RESULTS

A total of 230 dental implants were placed in 120 patients (67 males, 53 females; mean age 42.5 ± 10.8 years), with 60% in the maxilla and 40% in the mandible. Implant stability (ISQ) was highest among patients with the COL1A1 GG genotype (+3.62; 95% CI: 1.88–5.36; $p < 0.001$) and VDR CC genotype (+2.74; 95% CI: 0.96–4.52; $p = 0.003$). In contrast, IL-1β TT (−2.48; 95% CI: −4.31 to −0.65; $p = 0.009$) and TNF-α AA (−3.11; 95% CI: −5.08 to −1.14; $p = 0.002$) carriers showed reduced ISQ values as shown in table 1.

Table 1-Implant Stability (ISQ) by Genetic Marker

Genetic Marker	Favorable Allele	Adjusted β (95% CI)	p-value
COL1A1 GG	Yes	+3.62 (1.88–5.36)	<0.001
VDR CC	Yes	+2.74 (0.96–4.52)	0.003
IL-1β TT	No	−2.48 (−4.31–−0.65)	0.009
TNF-α AA	No	−3.11 (−5.08–−1.14)	0.002

As shown in table-2 marginal bone loss was significantly lower in BMP2 TT (−0.26 mm; 95% CI: −0.41 to −0.11; p = 0.001) and VDR CC (−0.19 mm; 95% CI: −0.34 to −0.04; p = 0.012) carriers. Individuals with IL-1β TT (+0.31 mm; 95% CI: 0.14–0.48; p = 0.001) and IL-6 GG (+0.28 mm; 95% CI: 0.09–0.47; p = 0.004) experienced greater bone loss.

Table 2-Marginal Bone Loss (mm) by Genetic Marker

Genetic Marker	Favorable Allele	Adjusted β (95% CI)	p-value
BMP2 TT	Yes	−0.26 (−0.41–−0.11)	0.001
VDR CC	Yes	−0.19 (−0.34–−0.04)	0.012
IL-1β TT	No	+0.31 (0.14–0.48)	0.001
IL-6 GG	No	+0.28 (0.09–0.47)	0.004

Prosthodontic complications were more frequent among carriers of IL-1β TT (AOR = 2.64; 95% CI: 1.18–5.89; p = 0.018), TNF-α AA (AOR = 3.12; 95% CI: 1.41–6.92; p = 0.005), and CD14 TT (AOR = 2.21; 95% CI: 1.02–4.78; p = 0.044). These results highlight the role of genetic polymorphisms in predicting both osseointegration and prosthodontic outcomes as shown in table 3.

Table 3: Prosthodontic Complications by Genetic Marker

Genetic Marker	Unfavorable Allele	Adjusted OR (95% CI)	p-value
IL-1β TT	Yes	2.64 (1.18–5.89)	0.018
TNF-α AA	Yes	3.12 (1.41–6.92)	0.005
CD14 TT	Yes	2.21 (1.02–4.78)	0.044

DISCUSSION

This study demonstrates significant associations between genetic polymorphisms and implant outcomes. Favorable alleles in COL1A1 and VDR enhance collagen synthesis, bone mineralization, and implant stability [15,17]. Conversely, pro-inflammatory variants in IL-1β, TNF-α, IL-6, and CD14 increased risk for bone loss and prosthetic complications [7,13]. The IL 1 composite genotype and IL 1RN variants were particularly predictive of peri-implantitis, consistent with prior meta-analyses [8,10]. Assessment of multiple genetic markers provides a more robust risk stratification than single gene analysis. The results further demonstrated that implant stability quotient (ISQ) values were consistently higher among patients harboring osteogenic gene variants, particularly COL1A1 and VDR polymorphisms, indicating enhanced bone–implant contact and early osseointegration. Radiographic analysis revealed significantly reduced marginal bone loss in these patients at both 6- and 12-month follow-up intervals, reinforcing the role of genetic regulation in bone remodeling dynamics [15,16,17]. These findings are clinically relevant, as early implant stability has been shown to correlate strongly with long-term prosthodontic success and patient satisfaction, especially in functionally loaded restorations [1,9]. The observed genetic influence on peri-implant bone preservation may explain inter-individual variability in implant outcomes despite standardized surgical and prosthetic protocols. It is important to emphasize that the 12-month follow-up period reflects early biological response and initial peri-implant bone remodeling rather than long-term implant survival. Osseointegration and marginal bone stability during the first year represent critical determinants of early implant success; however, extended longitudinal studies are required to determine whether these genetic associations persist over long-term functional loading.

Patient behavior further modifies outcomes. Smoking, poor oral hygiene, and low calcium intake increase peri-implant tissue inflammation, particularly in carriers of pro-inflammatory alleles, highlighting the importance of a combined genetic and behavioral approach [1,6,12]. Hence, the study includes comprehensive genetic and clinical analysis with standardized measurements, and incorporation of environmental modifiers [1,6,12,15]. Limitations of this study include the moderate sample size, which may limit detection of small genetic effects or complex multi-gene interactions despite adequate power for moderate associations. Additionally, the

12-month follow-up period primarily reflects early osseointegration and peri-implant tissue response rather than long-term implant survival. Furthermore, the population-specific genetic distribution may limit generalizability to other ethnic groups. Larger multicenter longitudinal studies are recommended to validate and expand upon these findings. Multicenter studies are recommended to validate findings [3,6]. Soft tissue parameters assessed in this study, including bleeding on probing, probing depth, and peri-implant mucosal health, were notably compromised in individuals carrying pro-inflammatory cytokine polymorphisms. These patients demonstrated heightened inflammatory responses, supporting evidence that genetically driven immune dysregulation contributes to peri-implant tissue breakdown [7,13]. Additionally, chronic inflammation has been linked with psychological stress and depressive states, which may further impair immune response and oral health behaviors, compounding implant risk. This multifactorial interaction emphasizes that peri-implant disease should be viewed not only as a localized inflammatory condition but as a complex biopsychosocial process influenced by genetics, behavior, and systemic factors.

Epigenetic regulation and gene-environment interactions emerge as critical factors influencing osseointegration and tissue response. These may explain variability in implant success among patients with similar genetic profiles. Integrating genetic profiling into clinical practice can improve treatment planning, prosthodontic design, and maintenance protocols. Personalized approaches informed by genotype and patient behavior can reduce complications and improve long-term success [3,9,15,17].

Conclusion

This study demonstrates that host genetic variability plays a critical role in determining the success of dental implants by influencing osseointegration, peri-implant tissue stability, and prosthodontic outcomes. Polymorphisms in genes associated with bone metabolism, particularly COL1A1, BMP2, and VDR, were strongly associated with higher implant stability values and reduced marginal bone loss, underscoring their importance in bone formation, collagen synthesis, and mineralization processes. These findings support the concept that favorable osteogenic genetic profiles contribute to predictable implant integration and long-term functional success.

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