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ASSOCIATION BETWEEN VITAMIN D RECEPTOR (VDR) GENE POLYMORPHISMS AND EARLY DENTAL IMPLANT OSSEOINTEGRATION: A PROSPECTIVE CLINICAL STUDY

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ABSTRACT

Background: Dental implant osseointegration is a multifactorial process influenced by surgical, prosthetic, and host-related determinants. Vitamin D, acting through the vitamin D receptor (VDR), regulates calcium homeostasis, osteoblast differentiation, and bone remodelling. Functional polymorphisms in the VDR gene may therefore modulate peri-implant bone healing and the development of early implant stability.

Aim: To evaluate the association between four common VDR gene polymorphisms—FokI (rs2228570), BsmI (rs1544410), ApaI (rs7975232) and TaqI (rs731236)—and early implant stability, and to explore the influence of serum vitamin D status on osseointegration.

Materials and Methods: One hundred systemically healthy adults receiving a single endosseous implant were enrolled prospectively. Genomic DNA extracted from peripheral blood was genotyped by PCR-RFLP for the four polymorphisms, and serum 25-hydroxyvitamin D was measured. Implant stability was recorded as the implant stability quotient (ISQ) by resonance frequency analysis at placement (primary stability) and at the second-stage/loading review (secondary stability); the gain in stability (ΔISQ) was calculated. Genotype frequencies were tested for Hardy–Weinberg equilibrium, and associations with ISQ and osseointegration outcome were assessed by ANOVA, chi-square, and multivariate regression ($p < 0.05$).

Results: All four polymorphisms were in Hardy–Weinberg equilibrium. Primary stability did not differ by genotype. The FokI polymorphism was significantly associated with ΔISQ (ANOVA $p = 0.002$): ff carriers showed a markedly smaller stability gain (3.31 ± 2.17) than FF (5.77 ± 2.34) or Ff (6.10 ± 2.50) carriers. In the adjusted linear model, the FokI ff genotype independently predicted a lower ΔISQ ($\beta = -2.52$; 95% CI −4.02 to −1.02; $p = 0.001$). BsmI, ApaI, and TaqI showed no significant association with any stability measure. Serum vitamin D did not correlate significantly with ISQ or osseointegration outcome in this cohort. Sixteen implants (16%) showed delayed osseointegration and five (5%) were early failures; the FokI ff genotype was associated with delayed osseointegration at a non-significant trend level (adjusted OR 3.67; 95% CI 0.83–16.2; $p = 0.086$).

Conclusion: Within the limits of this study, the VDR FokI polymorphism was independently associated with reduced early implant stability gain, whereas BsmI, ApaI, TaqI, and serum vitamin D level were not. VDR FokI genotyping may help identify patients at risk of slower osseointegration and merits evaluation in larger cohorts.

KEYWORDS: Dental implants; Osseointegration; Vitamin D receptor; Gene polymorphism; FokI; Implant stability quotient; Resonance frequency analysis.

1. INTRODUCTION

Osseointegration, defined as a direct structural and functional connection between ordered, living bone and the surface of a load-bearing implant, remains the biological foundation of predictable implant therapy. Contemporary implants demonstrate high long-term survival rates, yet a small but clinically important proportion fail to integrate. Early failures—those occurring before or at abutment connection—continue to challenge clinicians even when surgical protocols, implant design, and bone quantity appear adequate.

Early implant failure is widely regarded as multifactorial. Established contributors include smoking, uncontrolled diabetes, poor bone quality, surgical trauma, overheating during osteotomy, insufficient primary stability, and bacterial contamination. However, the observation that failures often cluster within particular individuals has directed attention towards host genetic factors that may govern the bone-healing response independently of these local variables.

Vitamin D occupies a central position in bone biology. Its active metabolite, 1,25-dihydroxyvitamin D3, regulates intestinal calcium and phosphate absorption, osteoblast and osteoclast activity, and the mineralisation of newly formed bone. Because the biological actions of vitamin D are mediated almost entirely through the vitamin D receptor (VDR), the efficiency of this signalling axis depends not only on circulating 25-hydroxyvitamin D concentration but also on the structure and expression of the receptor itself.

The VDR gene, located on chromosome 12q13.11, is highly polymorphic. Four restriction-site polymorphisms have been studied most extensively: FokI (rs2228570) in exon 2, which alters the length of the translated receptor protein; and BsmI (rs1544410), ApaI (rs7975232), and TaqI (rs731236) clustered near the 3′ region, which are thought to influence messenger RNA stability and gene expression. These variants have been repeatedly associated with bone mineral density, osteoporosis, and fracture risk, although findings differ across ethnic populations.

Given the pivotal role of VDR signalling in bone metabolism, it is biologically plausible that VDR polymorphisms modulate peri-implant healing and, therefore, the speed and predictability of osseointegration. Preliminary clinical work has produced conflicting results: some investigations found no association between VDR variants such as TaqI and implant loss, whereas others identified specific alleles as potential genetic risk markers. Parallel evidence links low serum vitamin D to an increased risk of early implant failure, though prospective data correlating VDR genotype with objective, quantitative measures of early implant stability remain limited.

Resonance frequency analysis (RFA), expressed as the implant stability quotient (ISQ), offers a non-invasive, reproducible method of monitoring implant stability from placement through healing. Tracking the change in ISQ over time (ΔISQ) captures the transition from mechanical (primary) to biological (secondary) stability and thus provides a clinically meaningful surrogate for osseointegration. The present prospective clinical study was designed to determine whether VDR FokI, BsmI, ApaI, and TaqI polymorphisms are associated with early implant stability, and to explore the combined influence of VDR genotype and serum vitamin D status on osseointegration outcomes in a systemically healthy adult population.

2. MATERIALS AND METHODS

2.1 Study design and setting

This prospective clinical study was conducted in the Department of Prosthodontics in collaboration with the participating institutions, over a defined enrolment period, and was reported in accordance with the Declaration of Helsinki and the STROBE recommendations for observational research.

2.2 Ethical approval and consent

Ethical clearance was obtained from the Institutional Ethics Committee prior to commencement [insert approval number and date]. The nature and purpose of the study were explained to every participant, and written informed consent was obtained before enrolment. Genetic data were anonymised and handled in accordance with institutional data-protection policy.

2.3 Sample size and participants

A total of 100 systemically healthy adults, each receiving one endosseous dental implant, were enrolled. The sample size was estimated a priori (G*Power v3.1.9.7) assuming a two-sided α of 0.05, power of 0.80, and a moderate effect size for the difference in stability between genotype groups, and was consistent with comparable VDR–implant studies.

2.4 Eligibility criteria

Inclusion criteria: systemically healthy adults aged 18–65 years; an edentulous site requiring a single endosseous implant ≥ 3.5 mm in diameter and ≥ 8 mm in length without adjunctive grafting; and ability to attend follow-up.

Exclusion criteria: uncontrolled diabetes or other disease affecting bone metabolism; current bisphosphonate, corticosteroid, or vitamin D supplementation; pregnancy or lactation; heavy smoking; previous head and neck radiotherapy; untreated periodontitis; and any site requiring simultaneous bone augmentation.

2.5 Surgical and prosthetic protocol

All implants were placed by experienced operators under local anaesthesia following a standardised drilling sequence with copious saline irrigation to avoid thermal injury. Implants of a single system and surface were used to minimise

device-related variability. Primary stability was recorded at placement, and the standard manufacturer healing period was observed before second-stage surgery and prosthetic loading.

2.6 Blood sampling, serum vitamin D, and DNA extraction

A peripheral venous blood sample was collected at enrolment. Serum 25-hydroxyvitamin D was measured by chemiluminescent immunoassay and classified as sufficient (> 30 ng/mL), insufficient (10–30 ng/mL), or deficient (< 10 ng/mL). Genomic DNA was extracted from peripheral leukocytes using a commercial column-based kit; DNA quantity and purity were verified spectrophotometrically (A260/A280).

2.7 VDR genotyping

FokI (rs2228570), BsmI (rs1544410), ApaI (rs7975232), and TaqI (rs731236) were genotyped by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) using the corresponding restriction endonucleases, following previously validated protocols. Approximately 10% of samples were re-genotyped in a blinded fashion to confirm reproducibility.

2.8 Assessment of osseointegration (implant stability)

Implant stability was quantified by resonance frequency analysis using an Osstell device and the appropriate SmartPeg. ISQ values (scale 1–100) were recorded in duplicate at two perpendicular positions and averaged. Primary stability was measured at placement and secondary stability at the second-stage/loading review; ΔISQ (secondary − primary) was calculated for each implant. Osseointegration was classified as successful (immobile, asymptomatic implant with an acceptable secondary ISQ and adequate stability gain), delayed (integrated but with a reduced or slow stability gain), or early failure (mobility, persistent pain, infection, or the need for removal before or at loading).

2.9 Statistical analysis

Data were analysed using standard statistical software. Genotype and allele frequencies were determined by direct counting, and conformity to Hardy–Weinberg equilibrium was tested by chi-square goodness-of-fit. Categorical variables were compared with the chi-square or Fisher's exact test and continuous variables (ISQ, ΔISQ, serum vitamin D) with the Student's t-test, one-way ANOVA, or Pearson correlation, as appropriate. Multivariate linear regression (outcome: ΔISQ) and logistic regression (outcome: delayed osseointegration) were used to assess the independent effect of VDR genotype after adjustment for age, sex, arch, bone quality, and serum vitamin D. A p-value < 0.05 was considered significant.

3. RESULTS

3.1 Study population

One hundred participants each receiving one implant completed the study. The mean age was 46.5 ± 13.5 years (range 20–65); 57 participants (57%) were female and 43 (43%) male. Fifty-three implants (53%) were placed in the maxilla and 47 (47%) in the mandible. Bone quality was predominantly D2 (44%) and D3 (34%). The mean serum 25-hydroxyvitamin D was 23.8 ± 9.9 ng/mL; 31 participants (31%) were vitamin D sufficient, 63 (63%) insufficient, and 6 (6%) deficient. The mean primary ISQ was 66.9 ± 3.9, secondary ISQ 72.5 ± 4.3, and ΔISQ 5.6 ± 2.5. Overall, 84 implants (84%) achieved successful osseointegration, 16 (16%) showed delayed osseointegration, and 5 (5%) were recorded as early failures (Table 1).

Table 1. Baseline demographic and clinical characteristics (N = 100).

Variable	Value	Category detail
Participants / implants	100 / 100	One implant per patient
Mean age (years)	46.5 ± 13.5	Range 20–65
Sex (Female / Male)	57 / 43	57% / 43%
Arch (Maxilla / Mandible)	53 / 47	53% / 47%
Bone quality (D1/D2/D3/D4)	11 / 44 / 34 / 11	Lekholm & Zarb
Serum 25(OH)D (ng/mL)	23.8 ± 9.9	Range 8.0–41.2
Vitamin D status (Suf/Insuf/Def)	31 / 63 / 6	31% / 63% / 6%
Primary ISQ	66.9 ± 3.9	At placement
Secondary ISQ	72.5 ± 4.3	At loading review

Variable	Value	Category detail
ΔISQ	5.6 ± 2.5	Secondary − primary
Outcome (Success/Delayed/Failure)	84 / 16 / 5	Delayed and failures overlap

3.2 VDR genotype and allele frequencies

Genotype distributions for all four polymorphisms conformed to Hardy–Weinberg equilibrium ($p > 0.05$), supporting the representativeness of the sample. The minor-allele frequencies were 0.32 (FokI f), 0.41 (BsmI b), 0.43 (ApaI a), and 0.42 (TaqI t), comparable with reported values for South Asian populations (Table 2).

Table 2. VDR genotype and allele frequencies with Hardy–Weinberg equilibrium (HWE).

Polymorphism	Genotypes, n (%)	Minor allele freq.	HWE p-value
FokI (rs2228570)	FF 48 (48) / Ff 40 (40) / ff 12 (12)	0.32	0.419
BsmI (rs1544410)	BB 33 (33) / Bb 52 (52) / bb 15 (15)	0.41	0.454
ApaI (rs7975232)	AA 33 (33) / Aa 49 (49) / aa 18 (18)	0.43	0.980
TaqI (rs731236)	TT 36 (36) / Tt 44 (44) / tt 20 (20)	0.42	0.333

3.3 Association of VDR genotypes with implant stability

Primary ISQ did not differ significantly among genotype groups for any polymorphism, consistent with primary stability being governed predominantly by bone quality and surgical technique. A significant difference emerged for the FokI polymorphism at the level of stability gain: ΔISQ differed across FokI genotypes (ANOVA $p = 0.002$), with ff carriers showing a substantially lower gain (3.31 ± 2.17) than FF (5.77 ± 2.34) and Ff (6.10 ± 2.50) carriers (Table 3). In a dominant comparison, ff carriers had a lower ΔISQ than FF/Ff carriers combined (3.31 ± 2.17 vs 5.92 ± 2.41; $p < 0.001$). Secondary ISQ showed a corresponding non-significant trend for FokI ($p = 0.095$). The BsmI, ApaI, and TaqI polymorphisms showed no significant association with ΔISQ (ANOVA $p = 0.590$, 0.777, and 0.757, respectively).

Table 3. Primary ISQ, secondary ISQ, and ΔISQ by VDR FokI genotype (mean ± SD).

FokI genotype (n)	Primary ISQ	Secondary ISQ	ΔISQ
FF (48)	66.68 ± 3.84	72.45 ± 4.29	5.77 ± 2.34
Ff (40)	67.23 ± 3.96	73.33 ± 4.18	6.10 ± 2.50
ff (12)	66.94 ± 3.83	70.25 ± 4.50	3.31 ± 2.17
ANOVA p-value	0.805	0.095	0.002

3.4 Serum vitamin D, genotype, and osseointegration

Serum 25-hydroxyvitamin D did not correlate significantly with primary ISQ ($r = 0.02$, $p = 0.82$), secondary ISQ ($r = 0.11$, $p = 0.30$), or ΔISQ ($r = 0.15$, $p = 0.15$). Vitamin D status was not significantly associated with osseointegration outcome (chi-square $p = 0.51$), and mean vitamin D did not differ between successful and delayed groups (24.1 ± 9.9 vs 22.4 ± 10.0 ng/mL; $p = 0.53$). As expected, implants with successful osseointegration had higher primary ISQ, secondary ISQ, and ΔISQ than those with delayed integration (all $p < 0.001$) (Table 4).

Table 4. Stability and vitamin D by osseointegration outcome (mean ± SD).

Parameter	Successful (n=84)	Delayed (n=16)	p-value
Primary ISQ	67.76 ± 3.58	62.59 ± 1.85	< 0.001
Secondary ISQ	73.79 ± 3.46	65.97 ± 1.76	< 0.001
ΔISQ	6.03 ± 2.41	3.38 ± 1.81	< 0.001
Serum 25(OH)D (ng/mL)	24.08 ± 9.92	22.38 ± 10.03	0.53

3.5 Multivariate analysis

In the multivariate linear regression for ΔISQ, the FokI ff genotype was the only significant independent predictor ($\beta = -2.52$; 95% CI −4.02 to −1.02; $p = 0.001$); age, sex, arch, bone quality, and serum vitamin D were not significant,

and the model explained 17% of the variance in ΔISQ. In the logistic model for delayed osseointegration, the FokI ff genotype showed an elevated but non-significant odds ratio (adjusted OR 3.67; 95% CI 0.83–16.2; p = 0.086), reflecting the small number of ff carriers and delayed cases (Table 5).

Table 5. Multivariate models for ΔISQ (linear) and delayed osseointegration (logistic).

Predictor	ΔISQ: β (95% CI), p	Delayed: OR (95% CI), p
FokI ff genotype	−2.52 (−4.02, −1.02), 0.001	3.67 (0.83, 16.2), 0.086
Age	−0.01 (−0.05, 0.02), 0.52	1.04 (0.99, 1.09), 0.098
Sex (male)	−0.84 (−1.84, 0.16), 0.097	0.96 (0.29, 3.19), 0.95
Arch (mandible)	0.58 (−0.39, 1.54), 0.24	1.68 (0.52, 5.40), 0.39
Bone quality (D1→D4)	−0.06 (−0.65, 0.53), 0.84	1.22 (0.60, 2.46), 0.58
Serum 25(OH)D	0.03 (−0.02, 0.08), 0.30	0.98 (0.93, 1.05), 0.60

4. DISCUSSION

This prospective study examined whether common VDR gene polymorphisms are associated with early dental implant stability, using resonance frequency analysis as an objective surrogate for osseointegration. The principal finding is that the FokI polymorphism—but not BsmI, ApaI, or TaqI—was significantly and independently associated with the gain in implant stability during healing, with ff carriers showing a markedly reduced ΔISQ.

Primary stability was unrelated to VDR genotype, which is expected because primary stability is a mechanical phenomenon dictated by bone density, implant macro-geometry, and surgical preparation rather than by the biological healing response. The relevance of VDR signalling became apparent during the transition to secondary stability, when de novo bone formation and remodelling at the implant surface depend on osteoblast recruitment and mineralisation—processes under vitamin D/VDR control. The association of the FokI variant with reduced stability gain is consistent with its functional significance: FokI alters the translation start site of the receptor, producing a longer, less transcriptionally active isoform in ff individuals, which may attenuate the osteogenic response at the peri-implant interface.

The absence of association for the 3′-region polymorphisms (BsmI, ApaI, TaqI) is compatible with earlier clinical work. Investigations from the Trevilatto group reported no significant association between the TaqI polymorphism and implant loss, and a recent case-control study likewise found no significant relationship between a VDR SNP and implant failure. Our results extend these observations by showing that, when a continuous and sensitive stability outcome (ΔISQ) is used rather than a binary failure endpoint, a genotype-dependent difference is nonetheless detectable—localised specifically to the functionally coding FokI variant.

Notably, serum vitamin D level did not correlate significantly with implant stability or osseointegration outcome in this cohort. This contrasts with several reports linking low serum vitamin D to early implant failure, but is consistent with the more equivocal picture in the wider literature, where a number of studies and a recent systematic review conclude that evidence for an independent vitamin D effect is inconsistent and limited by confounding. A likely explanation in the present sample is the restricted range and predominance of insufficient values (only six deficient participants), which limits statistical power to detect an effect of severe deficiency. Importantly, the FokI association persisted after adjustment for vitamin D, indicating that the genotype effect on early stability was not simply a proxy for circulating vitamin D status.

From a clinical standpoint, the FokI ff genotype showed an elevated odds ratio for delayed osseointegration (OR 3.67), although this did not reach statistical significance owing to the small number of ff carriers and delayed cases. If confirmed in larger cohorts, VDR FokI genotyping could contribute to individualised risk assessment, helping to identify patients likely to experience slower stability gain who might benefit from extended healing periods or modified loading protocols. Such genotype-informed approaches are consistent with the broader move towards personalised risk stratification in implant dentistry.

5. Limitations

Several limitations should be acknowledged. The sample of 100 implants, while adequate for the primary continuous outcome, was underpowered for the binary osseointegration endpoint and for detecting small effects of individual polymorphisms or gene–gene and gene–environment interactions; the wide confidence interval around the FokI odds ratio reflects this. Allele frequencies vary between ethnic groups, so the findings may not generalise beyond the studied population. ISQ is a validated but indirect measure of osseointegration and does not fully capture histological bone-to-implant contact. The follow-up focused on early osseointegration; longer-term survival and marginal bone loss

were not evaluated. Finally, unmeasured confounders such as dietary calcium intake, physical activity, and sun exposure may influence both vitamin D status and bone healing. Multicentre studies with larger, ethnically diverse cohorts and haplotype-level analysis are warranted.

6. CONCLUSION

Within its limitations, this prospective clinical study found that the VDR FokI polymorphism was independently associated with reduced early implant stability gain (ΔISQ), with ff carriers experiencing the smallest increase in stability during healing. The BsmI, ApaI, and TaqI polymorphisms and serum vitamin D level were not significantly associated with early stability in this cohort. Primary stability was independent of genotype, whereas the development of secondary stability appeared sensitive to VDR FokI status. These results suggest that VDR FokI genotyping may, in future, contribute to individualised assessment of osseointegration risk, and larger multicentre studies with longer follow-up are required to confirm the association and translate it into clinical practice.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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