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Original Article

Associations among gene polymorphisms, crestal bone loss, and bone mineral density in patients receiving dental implants

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المخلص

أهداف البحث: يستقصي هذا البحث تأثير تعدد أشكال الجينات لإنترلوكين ١ وإنترلوكين ٦ على كثافة المعادن في العظام وفقدان العظم الهامشي حول زراعة الأسنان. ومع ذلك، فإن تأثير كثافة المعادن بالعظام النظامية على تباين فقدان العظام الهامشي المحيط بالزرعة ليس واضحا. وبالتالي، تم إجراء هذه الدراسة للتحقق من ارتباط تعدد أشكال الجينات إنترلوكين ١ وإنترلوكين ٦ مع كثافة المعادن بالعظام الجهازية و فقدان العظام الهامشي حول زراعة الأسنان.

طرق البحث: شملت الدراسة ١٩٠ مشاركا تم اختيارهم لزراعة الأسنان في المنطقة الخلفية للفك السفلي. تم تصنيف المشاركين بناء على كثافة المعادن في العظام المقاسة بالأشعة السينية ثنائية الطاقة: كثافة المعادن الطبيعية في العظام (93 مشاركا)، معدل ت ≥ -1 كثافة المعادن المنخفضة في العظام بما في ذلك هشاشة العظام وترقق العظام (97 مشاركا)، معدل ت ≤ -1 الانحراف المعياري. تم وضع زرعات الأسنان وفقا للبروتوكولات الجراحية القياسية، وتم قياس فقدان العظم الهامشي بعد ٦ أشهر باستخدام المسح الطبقي المحوري قبل جراحة المرحلة الثانية. تم إجراء تحديد النمط الجيني لكافة المشاركين للجينات آي إل-1أ-889 أ/ج، آي إل-1ب-511 ج/أ، آي إل-1ب+3954 ، و آي إل-6-572 س/ج لتحليل تعدد أشكال الجينات.

النتائج: قارنت الدراسة الخصائص الديموغرافية والسريرية للمشاركين ذوي الكثافة العظمية الطبيعية والمنخفضة. وجدت الدراسة ارتباطات هامة بين تعدد أشكال الجينات إنترلوكين ١ وإنترلوكين ٦ وزيادة فقدان العظم الهامشي حول زرعات الأسنان لدى المشاركين ذوي الكثافة العظمية المنخفضة.

الاستنتاجات: كان الأفراد الذين يحملون الأنماط الجينية المعينة (إنترلوكين ١ب-٥١١ ألف ألف أو إنترلوكين ٦-٥٧٢ جي جي) في خطر متزايد للإصابة بترقق العظام أو هشاشة العظام. وكانوا أيضا أكثر عرضة لفقدان العظم الهامشي حول زرعات الأسنان.

الكلمات المفتاحية: تعدد أشكال الجينات؛ هشاشة العظام؛ زراعة الأسنان؛ كثافة العظم المنخفضة؛ فقدان العظم الهامشي المبكر

Abstract

Objectives: Interleukin 1 (IL-1) and interleukin 6 (IL-6) gene polymorphisms have been suggested to be responsible for diminished bone mineral density (BMD) and high crestal bone loss (CBL) in some individuals. However, the effects of systemic BMD on variations in peri-implant CBL are unclear. Hence, this study was aimed at investigating the association of IL-1 and IL-6 gene polymorphisms with systemic BMD and CBL around dental implants.

Methods: A total of 190 participants undergoing dental implantation in the mandibular posterior region were selected according to predetermined selection criteria and divided into a normal BMD group (NBD, 93 participants, T-score ≥ −1) and low BMD group (LBD, including both osteoporosis and osteopenia, 97 participants, T-score < −1 standard deviation) according to the BMD of the right femoral neck, measured with dual-energy X-ray absorptiometry. Dental implants were

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placed through the standard surgical protocol, and CBL was calculated after 6 months with cone beam computed tomography scans before second-stage surgery. Genotyping was performed on all participants for IL-1A-889 A/G, IL-1B-511G/A, IL-1B+3954, and IL-6-572 C/G gene polymorphisms.

Results: The demographic and clinical characteristics of the participants in both groups were compared with t-test and chi-square test (χ^2). The associations of NBD and LBD with the different genotypes and CBL was determined with odds ratios, and $p < 0.05$ was considered statistically significant. The frequency of IL-1B-511AA and IL-6-572 GG genotypes was significantly higher in LBD than in NBD ($p < 0.05$). In LBD, the IL-1B-511 AA (AA vs GA + GG; $p \leq 0.001$) and IL-6-572 GG (GG vs CC + GC; $p = 0.001$) genotypes were significantly associated with higher peri-implant CBL.

Conclusions: Individuals with the IL-1B-511 AA or IL-6-572 GG genotype had elevated risk of osteoporosis/osteopenia and were more susceptible to CBL around dental implants.

Keywords: Dental implants; Early crestal bone loss; Gene polymorphisms; Low bone density; Osteoporosis

Introduction

Osteoporosis is a generalized bone disease characterized by diminished mineral density and alterations in the bony tissue microarchitecture due to increased marrow space, thus making the bone fragile.[1] According to the World Health Organization (WHO), osteoporosis is characterized by a physiologic bone mineral density (BMD) 25 % lower than normal.[2] Osteoporosis is considered a relative contraindication for implant therapy because of delayed osseointegration and elevated crestal bone loss (CBL).[3] In contrast, several studies have observed no significant effect of low systemic bone density on CBL around dental implants.[4,5] Hence, the effects of systemic bone density on peri-implant CBL remains a matter of contention. The possibility that CBL around dental implants might be associated with genetic differences among individuals with systemic bone density must be explored. Therefore, this study was conducted to provide scientific evidence for this possibility. The null hypothesis was that no difference in the association of IL-1B-511 and IL-6-572 gene polymorphisms with ECBL would be observed around dental implants in individuals with normal and low systemic bone density.

Some studies have reported that polymorphisms of interleukin (IL) genes (primarily IL-1 and IL-6) may be responsible for diminished BMD[6] and high CBL in some individuals.[7,8] the proinflammatory cytokines IL-1 (IL-1A and 1B) and IL-6, which act as mediators in bone metabolism, along with various inflammatory responses,[9] are encoded by the IL-1 gene on chromosome 2 and the IL-6 gene on chromosome 7.[10] During dental implant placement, the surgical installation stimulates the initial inflammatory response. In the process, various cytokines and inflammatory mediators, including IL-1 and IL-6, are produced.[11] These cytokines play crucial roles in bone remodeling by inducing bone resorption.[12,13] This increased production of cytokines has been reported to be associated with polymorphisms in IL-1A889, IL-1B 511, IL-1B-3954, and IL-6 572G/C, thus increasing susceptibility to periodontitis and osteoporosis.[10,14] Studies have reported an association of polymorphisms in IL-1A889, IL-1B 511, and IL-1B-3954 with CBL, periimplantitis, and implant failure.[15]

In the current literature, little is known regarding the possible causative factors of occurrence and variation in CBL in people with aberrant bone density. People with osteoporosis are considered to have elevated risk of CBL around dental implants. However, controversy persists regarding the effects of systemic BMD on the occurrence and variation in CBL around dental implants. Herein, we sought to investigate and link single nucleotide polymorphisms (SNPs, DNA variations that may be responsible for diversity among individuals) in genes responsible for bone remodeling to CBL around dental implants. This examined SNPs in the IL-1 and IL-6 genes in individuals with aberrant bone density profiles, and to examine their relationship with early CBL around submerged dental implants.

Materials and Methods

This observational study was conducted in the Department of Prosthodontics, in collaboration with the Department of Oral Medicine and Radiology and the Center for Advance Research, at King George Medical University, Lucknow, India. Ethical approval was granted by the institutional ethical committee (1547/Ethics/R-Cell-17).

A total of 190 healthy participants visiting the department met the predetermined selection criteria and were enrolled in this study. The inclusion criteria were an age of 18−65 years; a single missing tooth in the mandibular posterior region; fully healed edentulous areas with sufficient bone volume (at least 11 mm height and 8 mm width), as determined with computed bone tomographic scans (CBCT); adequate width of keratinized mucosa; no medical contraindication to implant surgery; and provision of informed consent. The socio-demographic status of the participants and clinical data including BMD, bone quality, and torque were recorded. Lekholm & Zarb (1985) classification, which is based on the volume and quality of bone available for dental implant treatment, was used to classify the implant sites.[16]

BMD of the right femoral neck was measured (g/cm^2) for all participants with dual-energy X-ray absorptiometry (DEXA) (Hologic QDR 2000 densitometer) performed by a single trained X-ray technician.[17] T-scores obtained for all participants were used to group participants according to the following WHO criteria: normal BMD (NBD, 93 participants, T-score ≥ -1) and low BMD (LBD, including both osteoporosis and osteopenia, 97 participants, T-score < -1 standard deviation).[18]

After undergoing a routine surgical protocol, participants were given a prophylactic dose of antibiotics 1 h before

surgery, which was followed by local anesthesia with articaine with adrenaline (1:100,000). A standard flap approach to two-stage implant surgery was used to place dental implants (Myriad plus; Equinox Technologies) of 4.5 mm diameter and 9.5 mm length with a torque value of 30–40 Ncm at 20 rpm, after sequential drilling in all participants with a surgical template (Figure 1). ISQ values were recorded with RFA (Osstell, Integration Diagnostics, Göteborg, Sweden) to confirm implant torque values. No bone or soft tissue augmentation was performed in any participants. Flaps were sutured with 3-0 silk sutures (Ethicon, USA), and post-operative instructions regarding antibiotic and analgesic medication, maintenance of proper hygiene with 0.2 % chlorhexidine gluconate, avoiding hot, spicy, or hard food during the healing period, and care for the surgical area were given to the participants. Participants were recalled at 7 days postoperatively for removal of sutures and to evaluate surgical site healing. CBCTs were taken for the participants immediately after stage I surgery (baseline) and before stage II surgery (after 6 months), to measure the crestal bone levels. Digital Imaging and Communications in Medicine (DICOM) files were evaluated by two observers at different time points with the software application CS9300 (Carestream). The ECBL was calculated for each participant as the mean difference in values at the baseline and after 6 months, which were obtained by drawing lines from the top of the implant along the collar surface of each implant on the buccal, lingual, mesial, and distal sides to the first crestal bone to implant contact level (Figure 1).[19,20] Participants in the NBD and LBD groups were stratified according to the ECBL values around dental implants into clinically significant ECBL (>0.5 mm) and clinically non-significant ECBL (≤0.5 mm).[14]

For gene polymorphism analysis, a 5 ml peripheral blood specimen was collected from each participant, and DNA extraction from the specimen was performed with a QIamp DNA isolation kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions.[21] DNA with an absorption ratio A260/280 ≥ 1.8 was considered for further processing for TaqMan® SNP genotyping assays for IL-1A-889 (rs1800587), IL-1B-511 (rs16944), IL-1B-3854 (rs1143634), and IL-6-572 (rs1800796) according to the manufacturer's instructions.[21] Raw data obtained with an ABI Step OnePlus Real-Time PCR System were then analyzed in TaqMan genotype software. The genotype calls were evaluated with a threshold quality value of 0.94.[21] (Figure 2).

Data were statistically analyzed in SPSS 21.0. Continuous variables were compared with Student's t-test or analysis of variance, whereas categorical variables were analyzed with the chi-square test (χ^2). The associations of NBD and LBD with different genotypic and allelic frequencies of the studied genes were determined with odds ratios, and $p < 0.05$ was considered statistically significant.

Results

A total of 185 participants were statistically analyzed (LBD = 94, NBD = 91), because implant failures were observed in two participants because of improper hygiene leading to periimplantitis, and three participants did not return for the follow-up visit because of changes in residence. Gene polymorphism analysis and ECBL calculation were also performed for the 185 participants (Figure 3).

A comparison of the participants' clinical and demographic characteristics indicated that the LBD and NBD groups were statistically similar in age, sex, body weight category (WHO criteria), smoking status, torque value of implant placement, number of menopausal women, and bone quality at the implant site ($p > 0.05$); however, the mean difference in T score was statistically significant between groups ($t = 1.89$; $p = 0.061$) ($\chi^2 = 6.52$; $p = 0.011$) (Table 1).

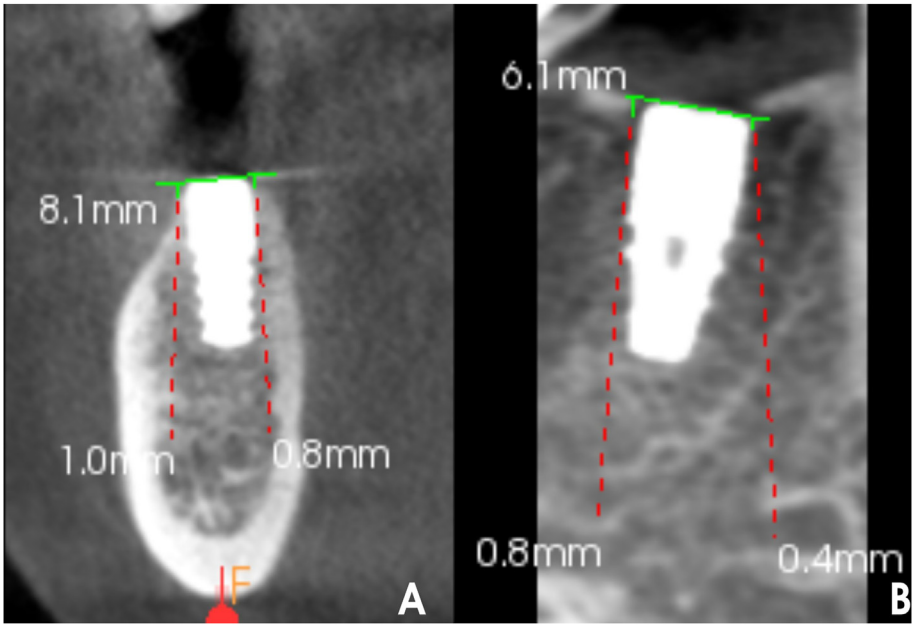

Figure 1: Measurement of CBL. A. Buccal and lingual side; B. mesial and distal side.

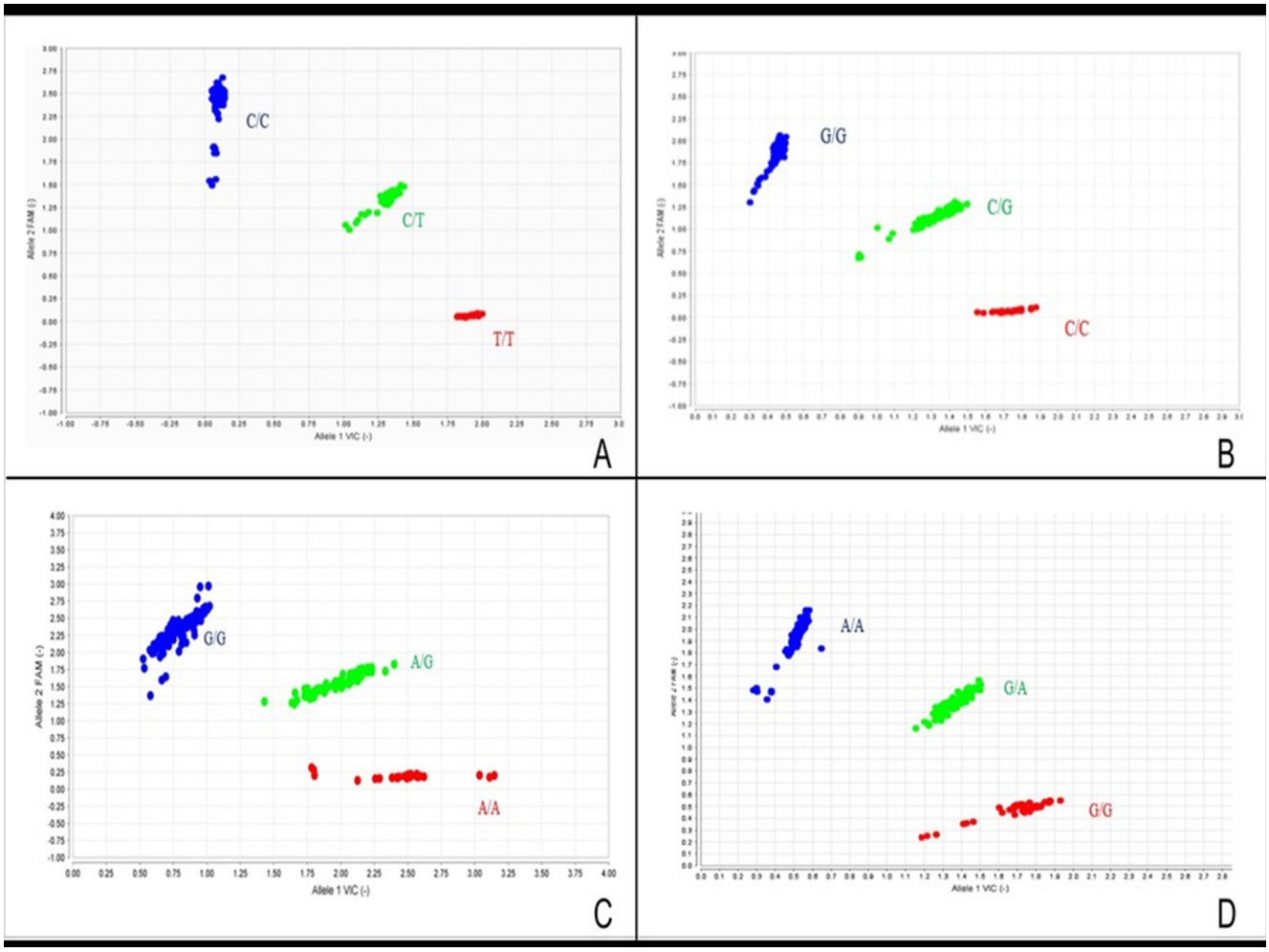

Figure 2: Gene polymorphism analysis. A. IL-1B+3954; B. IL-6-572 C/G; C. IL-1A-889 A/G; D. IL-1B-511G/A.

Table 2 shows the associations of both groups (NBD vs LBD) with different genotypic frequencies of the IL-1A889, IL-1B 511, IL-1B-3954, and IL-6-572 genes. For IL-1B-511, AA genotypes were associated with significantly higher odds of low BMD than GG genotypes [$p \leq 0.001$; OR = 17.47 (95 % CI = 3.62−84.32)]. The occurrence of low BMD was significantly higher among participants with AA genotypes than AG or GG genotypes ($\chi 2 = 18$, $p = < 0.001$). Similarly, CC genotypes of IL-6-572 were associated with significantly lower odds of low BMD than GG genotypes [$p = 0.002$; OR = 0.09 (95 % CI = 0.03−0.33)]. The occurrence of low BMD was significantly higher in participants with GG genotypes than CC or CG genotypes ($\chi 2 = 21.70$, $p \leq 0.001$).

Table 3 shows the association of the genotypic frequencies of IL-1A889, IL-1B 511, IL-1B-3854, and IL-6-572 with ECBL in NBD and LBD. Statistically significant differences were observed in the distribution of IL-1B 511 genotypes (AA vs GA + GG; OR = 23.56,95 % CI = 6.3−87.5, $p \leq 0.001$) and IL-6-572 genotypes (GG vs CC + GC; OR = 6.22, 95% CI = 2.42−18.1, $p = 0.001$) among participants of with clinically significant ECBL compared with clinically non-significant ECBL in the LBD group (Table 3).

Discussion

This research is the first to investigate and compare SNPs of the IL-1 and IL-6 genes in individuals with normal or low systemic bone density, and to determine the association of the genotypic frequencies of these genes with ECBL around dental implants in those individuals. The null hypothesis was that no difference would be observed in the association of IL-1B-511 and IL-6-572 gene polymorphisms with ECBL around dental implants in individuals with normal and low systemic bone density. The results clearly indicated associations of IL-1B-511 and IL-6-572 gene polymorphisms with ECBL around dental implants in patients with low bone density cases; therefore, the null hypothesis was rejected.

CBL plays an important role in determining the success of dental implant treatment and greatly affects long-term outcomes.[1,2] Various factors affect the levels of CBL, including bone quality, the degree of surgical trauma, implant design, loading protocol, and any diseases and medications potentially affecting the bone remodeling process.[2–4] Contrasting findings have been observed in the literature examining peri-implant CBL around submerged dental implants (early CBL before stage II surgery). These variations

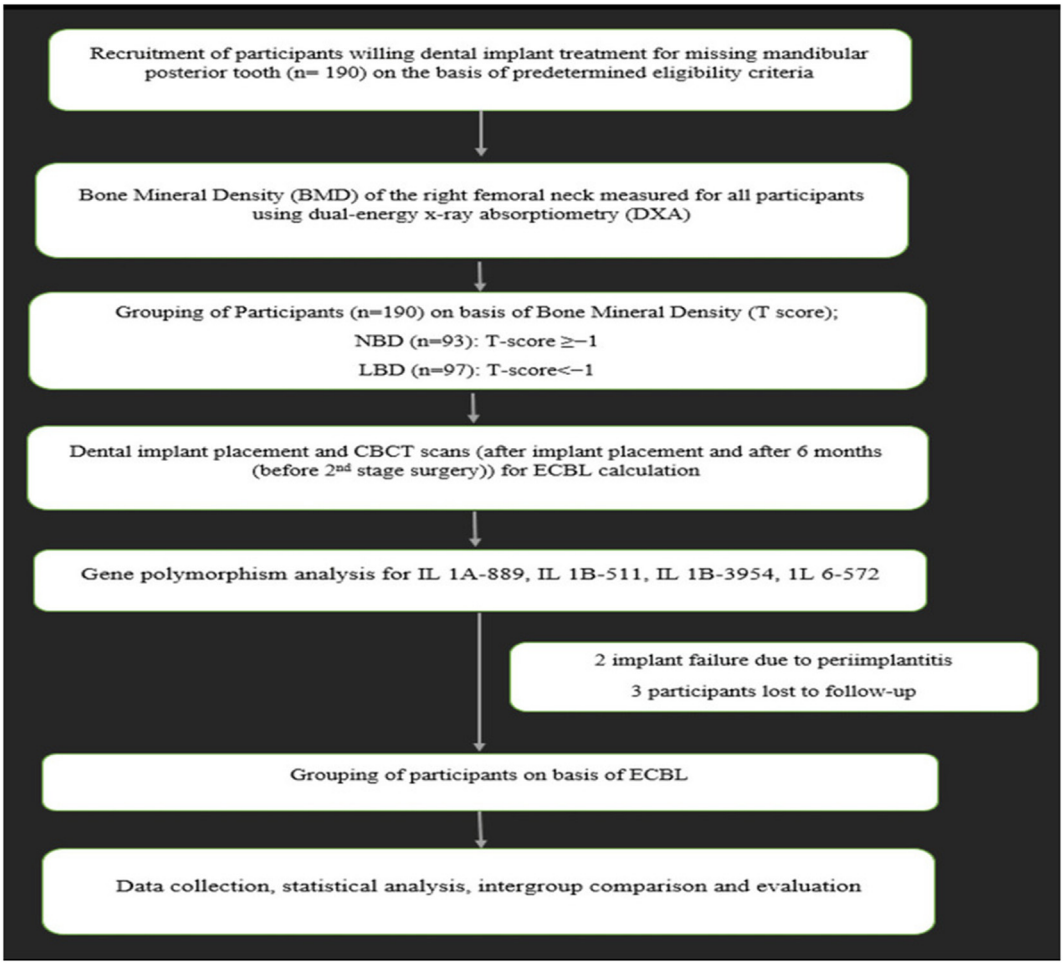

Figure 3: Study flowchart summarizing the group allocation and methods.

in ECBL may be attributable to differences among individuals in genes involved in bone remodeling. In our study, CBL was measured 6 months postoperatively before the placed implants were exposed to an oral environment, thereby minimizing the chances of infection.

To minimize the bias in the present study, we controlled for various confounders by maintaining homogeneity in both groups in relation to basic characteristics such as age; sex; T-score; mean BMD; smoking habits; and clinical parameters such as implant type and size, surgical protocol, and torque values. Study participants were of Indian origin, many studies have reported racial and ethnic variations in the frequencies of gene polymorphisms associated with genetic susceptibility to a specific disease. Therefore, investigating genotypic frequency in a specific ethnic group is imperative, and the result obtained from one ethnic group must not be generalized to another.[22]

CBCT and DEXA were used to evaluate changes in crestal bone levels and BMD, respectively. CBCT scans precisely evaluate bone quantity, because of its three-dimensional nature and sensitivity sufficient to quantify bone loss of 1 mm or less.[19,20,23] DEXA is the gold-standard technique for the estimation of BMD, because of its accuracy, precision, non-invasiveness, reproducibility, speed, and minimal radiation exposure.[24] The WHO has established various skeletal sites for DEXA diagnosis, namely the total hip, femoral neck, lumbar spine, and 33 % radius (wrist). Herein, we used the right femoral neck for evaluation, because this portion has a higher percentage of soft bone than the rest of the femur.

We observed elevated susceptibility to ECBL in the LBD group with AA genotypes of IL-1B-511. However, no significant association of ECBL with BMD was observed for the IL-1A- 889 and ILB+3984 genotypes. Previous studies have also reported that ECBL around implants is elevated in the IL-1B-511 AA genotype.[14,25,26] IL-1B-511 gene polymorphisms have been associated with resistance to bisphosphonate treatment in Paget's disease affecting bone, thus suggesting a role of IL-1B-511 gene polymorphism in osteoclast-induced bone loss. In contrast, other studies have reported no significant difference in IL-1B 511 gene polymorphism frequency between patients with low bone density rheumatoid arthritis and healthy controls.[27] The differences in findings may be attributable to the differences in ethnicity in the selected participants among studies.

Elevated susceptibility to ECBL was observed in individuals with LBD with the IL-6-572 G allele or GG genotype in the present study. A direct explanation for this association was not found in the current literature; however, Chen et al.[28] have reported that the IL-6 572C/G GG

Table 1: Demographic and clinical characteristics of participants with normal versus low bone mineral density (NBD versus LBD).

Characteristic	NBD		LBD		Statistical significance
Age (mean, SD)	44.86	14.59	48.88	16.88	t = −1.478; p = 0.142
Sex (n %)					
Male		55.4		44.6	χ^2 = 2.78; p = 0.095
Female		41.0		59.0	
BMI (mean, SD) in kg/m^2	25.14	4.25	24.45	4.73	t = 0.88; p = 0.376
Weight category (n %)					
N		51.6		48.4	χ^2 = 2.43; p = 0.488
O		49.1		50.9	
OB		57.1		42.9	
U		27.3		72.7	
T-score (mean, SD)	−0.18	0.77	−1.84	0.52	t = 14.75; **p = < 0.001**
Torque (mean, SD)	35.38	6.92	33.91	6.58	t = 1.26; p = 0.209
Smoking (n %)					
Yes		61.1		38.9	χ^2 = 1.24; p = 0.265
No		47.0		53.0	
Menopausal status (n %)					
Yes		26.9		73.1	χ^2 = 3.27; p = 0.071
No		50.0		50.0	
Bone quality (n %)					
I		66.7		33.3	χ^2 = 5.15; p = 0.076
II		54.0		46.0	
III		32.3		67.7	

Table 2: Associations of genetic polymorphisms among participants in both groups (NBD and LBD).

Gene	Genotype	LBD (%)	NBD (n %)	χ2 values (p-value)	OR (95 % CI)	p-value
IL-1A-889	A/A	7.5	12.5	1.00	Ref.	
	A/G	37.3	37.5	(0.604)	0.60 (0.17−2.09)	0.622
	G/G	55.2	50.0		0.54 (0.16−1.82)	0.483
IL-1B-511	A/A	49.3	26.6	18.00	Ref.	
	G/A	47.8	45.3	**(<0.001)**	1.76 (0.81−3.81)	0.212
	G/G	3.0	28.1		17.47 (3.62−84.32)	**< 0.001**
IL-1B +3954	C/C	56.7	51.6	0.45	Ref.	
	C/T	38.8	42.2	(0.800)	1.96 (0.59−2.44)	0.756
	T/T	4.5	6.2		1.54 (0.32−7.37)	0.887
IL-6-572	C/C	6.0	21.9	21.70	Ref.	
	C/G	37.3	59.4	**(<0.001)**	0.43 (0.13−1.47)	0.278
	G/G	56.7	18.8		0.09 (0.03−0.33)	**0.002**

Table 3: Association of ECBL with gene polymorphisms in participants with normal bone density and (NBD) and low bone density (LBD).

Gene (rs number)	Genotype	NBD				LBD			
		ECBL >0.5	ECBL ≤0.5	OR (95 % CI)	p-value	ECBL >0.5	ECBL ≤0.5	OR (95 % CI)	p-value
		n (%)	n (%)			n (%)	n (%)		
IL_1A_889	GG	45.2	54.5	0.686 (0.26−1.84)	0.617	62.2	46.7	1.88 (0.71−4.99)	0.307
(rs1800587)	AA + GA	54.8	45.5			37.8	53.3		
IL-1B_511	AA	19.4	33.3	0.48 (0.15−1.51)	0.326	78.4	13.3	23.56 (6.3−87.5)	**<0.001**
(rs16944)	AG + GG	80.6	66.7			21.6	86.7		
IL-1B_3854	CC	51.2	51.5	1.04 (0.38−2.68)	0.994	56.8	56.7	1.01 (0.38−2.65)	0.994
(rs1143634)	CT + TT	48.8	48.5			43.2	43.3		
IL_6_572	GG	25.8	12.9	2.52 (0.67−9.44)	0.279	75.7	33.3	6.22 (2.42−18.1)	**0.001**
(rs1800796)	CC + CG	74.2	87.1			24.3	66.7		

genotype may be associated with elevated risk of osteoporosis, because IL-6 gene polymorphisms may potentially upregulate the expression of RANKL on osteoblasts and lead to direct bone destruction.[29] In addition, associations of IL-6 gene polymorphisms with both chronic periodontitis and elevated risk of aggressive periodontitis have been reported.[30]

This study was the first to determine the associations among genetic polymorphisms, systemic bone density, and

peri-implant ECBL. The results indicated that IL-1B 511 and IL-6 gene polymorphisms are significantly associated with elevated susceptibility to osteoporosis/osteopenia. The elevated levels of cytokines (IL-1 and IL-6) in IL-1 B511 and IL-6 GG and the enhanced bone fragility in individuals with low rather than normal bone density significantly correlated with ECBL around dental implants. This knowledge may aid in the diagnosis of individuals with low BMD and a genetic predisposition to ECBL. Our findings may also guide clinicians in treatment planning, decision-making, and modifications required with respect to implant design and surface modifications to minimize ECBL.

In this study, we attempted to minimize bias by maintaining homogeneity in the two groups. However, a multicenter, long-term study with a larger sample size will be required to increase the authenticity of the data. In addition, further studies in a diverse ethnic pool may provide more credible data that can be generalized to larger populations. Moreover, polymorphisms in other genes controlling the bone remodeling process could be studied to determine their association with osteoporosis and bone loss around dental implants.

Conclusions

This study indicated significantly higher occurrence of low BMD in individuals with IL-1B-511 AA and/or IL-6-572 GG genotypes. No significant association was observed between early CBL and SNPs in the studied genes in individuals with normal BMD; however, in participants with low BMD (osteoporosis + osteopenia), the IL-1B-511 AA and IL-6 572GG genotypes were significantly associated with clinically significant early CBL around dental implants.

Study recommendations

The present study, despite its limitations, may aid in the diagnosis of individuals with a genetic predisposition to low BMD, and may guide clinicians in deciding on treatment plans, dental implant placement, or modifying treatments with respect to implant design and surface modifications to minimize ECBL.

Source of funding

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

Ethical approval was granted by the institutional ethical committee of King George Medical University, Lucknow, India 226003 (1547/Ethics/R-Cell-17).

Consent

Written informed consent was obtained from all participants in the study.

Authors contributions

KKA: Concept/design, data acquisition, data analysis/interpretation, final article. NS: Concept/design, data acquisition. PC: Concept/design, drafting article, supervision. SVS: Data acquisition, drafting article, supervision. NS: Data acquisition, data analysis/interpretation. RKG: Concept/design, supervision. AC: Data acquisition, supervision. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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