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ORIGINAL RESEARCH

Chemokine Receptor 2 (CXCR2) Gene Polymorphisms and Their Association with the Risk of Developing Peri-Implantitis in Chinese Han Population

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Purpose: This study aimed to investigate the role of chemokine receptor 2 (*CXCR2*) gene polymorphisms in peri-implantitis susceptibility in a Chinese Han population.

Patients and Methods: A total of 260 individuals were included in this study, including 127 peri-implantitis patients and 133 healthy implants. *CXCR2* gene rs2230054 and rs1126580 polymorphisms in different groups were analyzed by the Chi-square test. The odds ratios (ORs) and 95% confidence intervals (95% CIs) were employed to evaluate the association between *CXCR2* polymorphism and peri-implantitis susceptibility.

Results: The CT genotype of rs2230054 and the AG genotype and G allele of rs1126580 significantly increased in peri-implantitis patients compared with healthy implants ($P < 0.05$). The CT genotype of rs2230054 (OR = 1.825, 95% CI = 1.028–3.239) and the AG genotype of rs1126580 (OR = 2.223, 95% CI 1.272–3.885) carriers had a high risk to infect with peri-implantitis. Additionally, these *CXCR2* gene polymorphisms have been revealed to be associated with the periodontal status of peri-implantitis patients.

Conclusion: The CXCR2 gene rs2230054 and rs1126580 polymorphisms were associated with the peri-implantitis susceptibility in the Chinese Han population. The CT genotype of rs2230054 and the AG genotype and G allele of rs1126580 serve as risk factors for the occurrence of peri-implantitis.

Keywords: chemokine receptor 2, *CXCR2*, polymorphism, peri-implantitis, Han population

Introduction

Dental implants are common options for patients who need the treatment of partial or total edentulism.[1] Peri-implantitis is an irreversible chronic inflammatory, which is one of the major causes of the failure in implant dentistry and is prevalent in patients that received dental implant.[1,2] The diagnosis of peri-implantitis depends on the bone loss and bleeding on probing with or without concomitant and the presence of purulent drainage.[3] There are a variety of risk factors that may attribute to peri-implantitis, including systemic conditions, environmental factors, history of periodontitis, and implant materials.[4,5] Additionally, the genetic trait has also been considered as an etiology of peri-implantitis, as the genetic variations could affect the function of genes.[6] The significant association between cytokine gene polymorphism, such as CD14, TNFα, and IL-6, and peri-implantitis risk in the Serbian

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population have been indicated in the previous study.[7] The identification of a marker that correlated with the development of peri-implantitis is of great importance in the clinic to improve the management of peri-implantitis.

Interleukin-8 (IL-8) is a proinflammatory cytokine.[8] By binding to Chemokine Receptor 2 (*CXCR2*), IL-8 could initiate chemotaxis, induce angiogenesis, stimulate cell proliferation, mediate hypernociception, and increase the concentration of calcium in various functional cells.[9] Single-nucleotide polymorphisms (SNPs) in gene sequences could alter the transcription of gene or the function of encoded protein, which may account for the pathogenesis of human disease.[10] *CXCR2* is located on 2q35, of which the gene polymorphisms have been revealed to be associated with the susceptibility of various diseases, such as stroke in patients with essential hypertension, prostate cancer, and systemic sclerosis.[11–13] *CXCR2* gene has been demonstrated to be expressed in oral epithelial cells.[14] Kavrikova et al have reported that *CXCR2* gene variants are correlated with the subgingival Gran-negative bacteria in chronic periodontitis patients, which is the major cause of periodontitis.[15] Therefore, *CXCR2* was speculated to be involved in the pathogenesis of peri-implantitis.

The *CXCR2* gene + 785C/T (rs2230054) and the *CXCR2* + 1440G/A (rs1126580) are two common SNPs of *CXCR2*. In this study, the genotypes were analyzed in these two SNPs in peri-implantitis patients and healthy controls in the Chinese Han population, to calculate the association of these SNPs with the susceptibility of peri-implantitis.

Patients and Methods

Subjects

A total of 127 patients diagnosed with peri-implantitis and 133 individuals with healthy implant were recruited in this study from 2017–2019. The basic clinical characteristics of the study subjects are summarized in Table 1. The periodontal evaluation was performed through a series of corresponding parameters, including gingival index, plaque index, calculus index, peri-implant pocket depth, and clinical attachment level, which have been listed in Table 2. All patients included in this study are Chinese Han population and attended to regular implant maintenance therapy at 6, 12, and 24 months after the loading of implants. The peri-implantitis patients were included according to the previous definition of peri-

Table 1 Basic Clinical Characteristics of the Study Population

Variables	Healthy Implants (n = 133)	Peri-Implantitis (n = 127)	*P* value
Age, mean ± SD	43.42 ± 6.31	44.07 ± 6.05	0.398
IL-8 (pg/mL), mean ± SD	48.16 ± 20.81	513.95 ± 63.20	< 0.001
MIP1-α (pg/mL), mean ± SD	7.23 ± 2.26	148.35 ± 36.01	< 0.001
Gender, n (%)			0.874
Male	72 (54.1)	70 (55.1)	
Female	61 (45.9)	57 (44.9)	
Alcohol consumption, n (%)			0.955
Yes	54 (40.6)	52 (40.9)	
No	79 (59.4)	75 (59.1)	
History of periodontitis, n (%)			0.034*
Yes	59 (44.4)	73 (57.5)	
No	74 (55.6)	54 (42.5)	
Platform type, n (%)			0.485
External hex	64 (48.1)	56 (44.1)	
Internal hex	20 (15.0)	28 (22.0)	
Morse cone	40 (30.1)	37 (29.1)	
Others	9 (6.8)	6 (4.7)	
Position, n (%)			0.068
Anterior region	89 (66.9)	71 (55.9)	
Posterior region	44 (33.1)	56 (44.1)	
Peri-implant phenotype, n (%)			0.269
Thin	73 (54.9)	61 (48.0)	
Thick	60 (45.1)	66 (52.0)	
Brushing daily, n (%)			0.538
1–3 times	115 (86.5)	113 (89.0)	
More than 3 times	18 (13.5)	14 (11.0)	
Dental floss daily, n (%)			0.284
Yes	50 (37.6)	54 (42.5)	
No	25 (18.8)	15 (11.8)	
Infrequent	58 (43.6)	58 (45.7)	

(*Continued*)

Table 1 (Continued).

Variables	Healthy Implants (n = 133)	Peri-Implantitis (n = 127)	*P* value
Mouth washing daily, n (%)			0.346
Yes	40 (30.1)	49 (38.6)	
No	31 (23.3)	25 (19.7)	
Infrequent	62 (46.6)	53 (41.7)	
Smoking			0.984
Yes	64 (48.12)	60 (47.44)	
No	69 (51.88)	67 (52.56)	

Notes: *P* value reflects the significance of the difference between the healthy implants and peri-implantitis groups, and the *P* value less than 0.05 was considered to be statistically significant.

implantitis and peri-implant health[16,17] and details are as follows: the presence of one or more implants with the loading period of more than 12 months; the presence of bleeding probing and the probing pocket depths > 4mm; the presence of crestal bone loss in at least one area around an implant; exposure of at least two edges of the implant. The exclusion criteria for enrolling patients were a history of systemic disease or occlusal trauma and the use of prophylactic antibiotics or anti-inflammatory drugs. The healthy individuals had no history or clinical signs of peri-implantitis; had a probing pocket depth < 3mm; had no radiographic signs of peri-implant bone resorption. This study was approved by the ethics committee of Zhongshan hospital (2016–145), Fudan university and was in accordance with the Declaration of Helsinki. All participants provided written informed consent before the sample collections.

Table 2 Periodontal Status of the Studied Population

Variable	Healthy Implants (n = 133)	Peri-Implantitis (n = 127)	*P* value
Gingival index	0.45 ± 0.21	2.48 ± 0.30	< 0.001
Plaque index	0.83 ± 0.44	2.35 ± 0.35	< 0.001
Calculus index	0.26 ± 0.17	0.44 ± 0.20	< 0.001
PPD (mm)	1.96 ± 0.35	5.58 ± 0.53	< 0.001
CAL (mm)	1.33 ± 0.35	4.88 ± 0.39	< 0.001

Notes: *P* value reflects the significance of the difference between the healthy implants and peri-implantitis groups, and the *P* value less than 0.05 was considered to be statistically significant.
Abbreviations: PPD, peri-implant pocket depth; CAL, clinical attachment level.

Table 3 Primer Sequences of CXCR2 Gene rs2230054 and rs1126580 Polymorphisms

Variations	Primer Sequences
rs2230054	Forward 5′-TCGTCCTCATCTTCCCGCT-3’
	Reverse 5′-GGAGTCCATGGCGAAACTTC-3’
rs1126580	Forward 5′-AGGCTGGCCAACGGGG/A-3’
	Reverse 5′-TCATAGCAGCTTATTCACAAGAC-3’

Sample Collection

Buccal epithelial cell samples were collected from each participant. Briefly, patients first gargled with 3% glucose solution, and scrape oral mucosa with a sterile wood spatula. The tip of the spatula was immediately shaken into the mouthwash solution and centrifugated at 2000 g for min to obtain buccal epithelial cells. The genomic DNA was extracted from collected buccal epithelial cell samples with the QIAamp DNA Mini Kit (QIAGEN, Germany) according to the manufacturer’s protocol. The genomic DNA was stored at −80°C.

Genotyping

The genotypes of SNPs in the *CXCR2* gene were examined using the polymerase chain reaction method (PCR). PCR was performed in a volume of 25 μL, including 100 ng DNA, 0.5 μM primers, 4 U of Taq DNA polymerase, 2mM buffer, and 0.5 mM deoxyribonucleoside triphosphate mix. The reaction condition was as follows: denaturation for 5 min at 95°C followed by 35 cycles of 95°C for 1 min, annealing at 58°C for 1 min, 72°C for 1 min, and a final extension at 72°C for 7 min. The primer sequences of + 785C/T (rs2230054) and + 1440G/A (rs1126580) were summarized in Table 3.

The purification of PCR products was conducted with ExoSAP-IT (USB Corp) and sequenced with an Applied Biosystems 3730×l automated sequencer (Applied Biosystems, Foster City, CA, USA), and all sequences were analyzed by Vector NTI software.

Statistical Analysis

Statistical analyses were performed with the PASW Statistical 18.0 statistical software. The genotype and allele frequencies for rs2230054 and the rs1126580 were calculated by direct counting. Hardy–Weinberg equilibrium (HWE) of each polymorphism was tested to assess the representativeness of the study population. The distributions of the

genotypes and allele of rs2230054 and rs1126580 in different groups were compared by the Chi-square test. The association between *CXCR2* polymorphism and peri-implantitis susceptibility was evaluated by the odds ratios (ORs) and 95% confidence intervals (95% CIs). $P < 0.05$ was considered to be statistically significant.

Results

Characteristics of the Study Subjects

The basic clinical characteristics of the study population are summarized in Table 1. 127 peri-implantitis patients were composed of 70 males and 57 females with the average age of 44.07 ± 6.05, which showed no significant difference with that of healthy implants ($P > 0.05$). Meanwhile, alcohol consumption, platform type, position, peri-implantitis, brushing daily, dental floss daily, mouth washing daily, and smoking habit between peri-implantitis and healthy implants were not significantly different ($P > 0.05$). However, the history of periodontitis of peri-implantitis patients was dramatically frequent than in healthy implants ($P = 0.034$). The concentration of chemokines, including IL-8 ($P < 0.001$) and MIP1-α ($P < 0.001$), was significantly higher in peri-implantitis patients than that of healthy implant.

For the periodontal status of participants, peri-implantitis patients possessed much higher scores of the gingival index, plaque index, calculus index than that of healthy implants ($P < 0.001$, Table 2). Moreover, the peri-implant pocket depth and the clinical attachment level of peri-implantitis patients were also significantly larger than that of healthy implants ($P < 0.001$, Table 2).

Association of *CXCR2* Polymorphisms with the Risk of Peri-Implantitis

Both the distribution of the genotype and allele of *CXCR2* gene rs2230054 and rs1126580 polymorphisms in healthy implants did not deviate from HWE, indicating the good representativeness of the study subjects ($P^{HWE} > 0.05$, Table 4).

For rs2230054 polymorphism, the frequency of CT genotype significantly increased in peri-implantitis patients compared with healthy implants (64.6% vs 51.9%, $P = 0.039$). Individuals with CT genotype showed a high risk of peri-implantitis (OR = 1.825, 95% CI = 1.028–3.239). Similarly, in rs1126580 polymorphism, the AG genotype frequency dramatically increased in peri-implantitis ($P = 0.005$) and AG genotype indicated a high risk of peri-implantitis (OR = 2.223, 95% CI = 1.272–3.885). Moreover, the G allele of rs1126580 significantly increased in peri-implantitis compared with healthy implants, which was correlated with the susceptibility of peri-implantitis (OR = 1.441, 95% CI = 1.015–2.046).

Table 4 Genotype and Allele Frequencies of *CXCR2* Gene rs2230054 and rs1126580 Polymorphisms Between Healthy Implants and Peri-Implantitis Groups

Genotype/Allele	Healthy Implants n=133 (%)	Peri-Implantitis n=127 (%)	χ^2	*P*	OR (95% CI)
rs2230054					
CC	43 (32.3)	28 (22.0)	–	–	1
CT	69 (51.9)	82 (64.6)	4.271	0.039*	1.825 (1.028–3.239)
TT	21 (15.8)	17 (13.4)	0.287	0.592	1.243 (0.560–2.759)
C	155 (58.3)	138 (54.3)	–	–	1
T	111 (41.7)	116 (45.7)	0.820	0.365	1.174 (0.830–1.661)
P^{HWE}	0.441				
rs1126580					
AA	53 (39.8)	30 (23.6)	–	–	1
AG	62 (46.6)	78 (61.4)	7.990	0.005*	2.223 (1.272–3.885)
GG	18 (13.5)	19 (15.0)	2.450	0.118	1.865 (0.851–4.088)
A	168 (63.2)	138 (54.3)	–	–	1
G	98 (36.8)	116 (45.7)	4.180	0.041*	1.441 (1.015–2.046)
P^{HWE}	0.984				

Notes: $P^{HWE} > 0.05$ means study population conforms to Hardy–Weinberg equilibrium; *P* value reflects the significance of the difference between the healthy implants and peri-implantitis groups, and the P value less than 0.05 was considered to be statistically significant.
Abbreviations: *CXCR2*, chemokine receptor 2; HWE, Hardy–Weinberg equilibrium.

Table 5 Association Analysis of *CXCR2* Gene Polymorphisms with Periodontal Status

Genotype	No.	Gingival Index		Plaque Index		Calculus Index		PPD (mm)		CAL (mm)	
		Mean ±SD	*P* value	Mean ±SD	*P* value	Mean ±SD	*P* value	Mean±SD	*P* value	Mean±SD	*P* value
rs2230054			0.031*		0.083		0.199		0.188		0.115
CC	71	1.20±0.97		1.43±0.82		0.33±0.17		3.42±1.82		2.71±1.74	
CT	151	1.59±1.02		1.67±0.84		0.37±0.21		3.90±1.89		3.25±1.82	
TT	38	1.45±1.10		1.44±0.97		0.30±0.27		3.61±1.85		2.97±1.89	
rs1126580			0.003*		0.035*		0.029*		0.040*		0.015*
AA	83	1.15±0.94		1.38±0.93		0.30±0.19		3.30±1.79		2.59±1.701	
AG	140	1.63±1.01		1.68±0.83		0.37±0.19		3.95±1.89		3.31±1.83	
GG	37	1.56±1.12		1.59±0.96		0.34±0.28		3.85±1.85		3.17±1.88	

Note: *$P < 0.05$.
Abbreviations: *CXCR2*, chemokine receptor 2; PPD, peri-implant pocket depth; CAL, clinical attachment level.

Association of *CXCR2* Polymorphisms with the Periodontal Status of Peri-Implantitis Patients

The association between *CXCR2* polymorphisms and the periodontal index of healthy implant and peri-implantitis patients was evaluated. As shown in Table 5, rs2230054 and rs1126580 genotype significantly affected the gingival index of peri-implantitis ($P < 0.05$), while the rs2230054 CT carriers and the rs1126580 AG carriers had a higher gingival index than other genotype carriers. Additionally, the rs1126580 AG genotype of *CXCR2* also exerted markable effects on the plaque index, calculus index, peri-implant pocket depth, and clinical attachment level of peri-implantitis patients ($P < 0.05$).

Discussion

Peri-implantitis is a primary cause of the failure in implant dentistry.[18] Multiple factors have been suggested to influence the occurrence of peri-implantitis, such as occlusal factors, general condition, smoking as well as oral health habit.[19] Among various risk factors, the role of genetic traits in the pathogenesis and development of peri-implantitis has drawn special attention. For example, Zhou and Zhao demonstrated people carrying the CC genotype of osteoprotegerin gene rs2073618 polymorphism are more likely to infect peri-implantitis than other genotype carriers.[20] The polymorphic variant rs1342913 BRINP3 showed a significant association with the peri-implantitis.[21] *CXCR2* has been reported to express in a wide range of leukocytes and to mediate a variety of biological activities, including inflammatory reaction, tumor growth, and metastasis. For instance, *CXCR2* was suggested to regulate cell proliferation, invasion, and angiogenesis of pancreatic cancer and suppress tumor progression via disrupting interactions between tumor cells and fibroblasts.[22–25]

Recently, *CXCR2* polymorphism has been associated with various diseases. The *CXCR2* rs1126579 polymorphism was associated with the risk of ischemic stroke, whereas the CC genotype was protective against stroke.[12] In the present study, the potential relevance of rs2230054 and rs1126580 polymorphisms in *CXCR2* with the risk of peri-implantitis was investigated in a Chinese Han population. The significant difference was found in the rs2230054 and the rs1126580 genotypes between peri-implantitis and healthy implants. The frequency of CT genotype in rs2230054 and the AG genotype and G allele in rs1126580 significantly increased in peri-implantitis patients indicating that these genotypes and alleles might serve as risk factors for the onset of peri-implantitis whereas the role of *CXCR2* polymorphisms was distinct in different populations. Kavrikova et al analyzed the association of *CXCR2* gene variants with periodontal bacteria in patients with chronic periodontitis in the Czech population and found that the C allele of rs2230054 and the T allele of rs1126579 in men were closely associated with *Aggregatibacter actinomycetemcomitans*, the main etiological agent of periodontitis.[15] In the Brazilian population, among three SNPs of the *CXCR2* gene, including rs2230054, rs1126579, and rs1126580, only rs1126580 showed significant association with periodontitis of patients.[26]

Further, the history of periodontitis is also an important risk factor for peri-implantitis. Previous studies have reported that patients with a history of periodontitis might be at high risk for peri-implantitis.[27] Here, the history of periodontitis was demonstrated to be significantly different between healthy implants and peri-implantitis and the periodontal status of the studied population was also obviously unequal, which is consistent with previous studies. Additionally, rs1126580 polymorphism was found to be associated with the periodontal status of peri-implantitis patients, including the gingival index, plaque index, calculus index, peri-implant pocket depth, and clinical attachment level. While rs2230054 polymorphism was associated with the gingival index of peri-implantitis patients. These periodontal clinical parameters were always applied to assess the health of peri-implant tissues in the clinic. Therefore, these results suggested that the rs2230054 and rs1126580 polymorphisms of the *CXCR2* gene were risk factors of peri-implantitis and were speculated to predicate peri-implantitis susceptibility.

The limitation of this study was the studied population was not large enough to achieve nominal significance. As this is a hospital-based case-control and cross-sectional study, the recruited population may not be representative of the general population. More representative studies are required to confirm the role of *CXCR2* gene polymorphisms in peri-implantitis in various populations.

Taken together, our results revealed that the rs2230054 and rs1126580 polymorphisms of the *CXCR2* gene were closely correlated with peri-implantitis susceptibility in the Chinese Han population. The CT genotype in rs230054, the AG genotype and G allele in rs1126580 were potential risk factors for the occurrence of peri-implantitis.

Abbreviations

CXCR2, Chemokine Receptor 2; ORs, odds ratios; CIs, confidence intervals; IL-8, Interleukin-8; SNPs, Single-nucleotide polymorphisms; PCR, polymerase chain reaction method; HWE, Hardy–Weinberg equilibrium.

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Disclosure

The authors report no conflicts of interest in this work.

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