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Haplotypes in BMP4 and FGF Genes Increase the Risk of Peri-Implantitis

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Despite the success of osseointegrated implants, failures have increased significantly, associated with development of peri-implantitis. Multiple factors influence the peri-implant bone loss, including environmental and genetic causes. BMPs (Bone morphogenetic proteins) are growth factors that induce bone formation. FGF (fibroblast growth factors) and their receptors (FGFRs) play important roles by controlling the levels of cell proliferation, differentiation and migration. BMP/FGF relationship is responsible for promoting bone regeneration and bone loss. The aim of this study was to analyze the correlation between BMP4, FGF3, FGF10 and FGFR1 genes and peri-implant bone loss. Two hundred and fifteen volunteers, with 754 dental implants, were submitted to oral examination and divided in healthy group (n=129) and peri-implantitis group (n=86). Thirteen polymorphisms in BMP4, FGF3, FGF10 and FGFR1 genes were analyzed individually and in haplotype. The chi-square test correlated genotypes, allelic and haplotype frequencies. Values of $p<0.05$ were considered significant. Volunteers with peri-implantitis demonstrated high incidence of total edentulism ($p<0.0001$) and thin peri-implant phenotype ($p<0.04$). Higher incidence of spontaneous bleeding, plaque and implant mobility was observed in peri-implantitis group ($p<0.0001$ for all). The TT polymorphic genotype for BMP4 rs2761884 was associated with healthy peri-implant ($p=0.01$). FGF3 rs4631909 (TT+CT genotype) also showed association with the control group ($p=0.04$). The frequency of C allele for FGF3 rs4631909 showed a tendency for association with peri-implantitis ($p=0.08$). FGF10 CCTG ($p=0.03$), BMP4 GAAA ($p=0.05$) and GGGA ($p=0.02$) haplotypes were associated with peri-implantitis ($p=0.03$). Therefore, it may be concluded that BMP4 and FGF10 haplotypes are associated with peri-implantitis.

Key Words: peri-implantitis, polymorphism, haplotype, FGF, BMP

Introduction

Osseointegrated oral implants have been widely used as first-line therapy in cases of total or partial dental arch rehabilitation (1). However, despite the reported high success rate, failures in implant dentistry have a significant increase because of peri-implantitis development, characterized by the pathological resorption of adjacent bone to the endosseous implant and may result in implant loss (2). This process of bone loss is influenced by a multitude of factors, some of which are understood while others are still unknown and share several environmental and genetic causes (3). Recent studies have associated peri-implantitis with the host's destructive inflammatory response characterized by the high expression of proinflammatory cytokines and osteoclast activation (4).

In bone repair, the biological response to bacterial or traumatic tissue damage can result in wound healing or culminate in advanced bone loss. Hematoma formation during bone regeneration is the basis for bone repair. The release of growth factors, including platelet-derived growth factors (PDGF), tumor growth factor type-β (TGF-β), interleukins (IL) 1 and 6, during inflammatory response increase osteoprogenitor cells and fibroblasts proliferation and are associated with bone morphogenetic proteins (BMP) and fibroblast growth factors (FGF) expressions. As the hematoma matures, a collagen matrix develops with neovascularization, providing a scaffold for these cells (5). When this regenerative ability fails to maintain osseointegration by a cascade of bone remodeling processes, the stimulation of bacterial presence associated with intrinsic factors triggers pathological bone loss (6).

BMPs (bone morphogenetic proteins) are growth factors and belong to the TGF-β superfamily located in chromosome 14q22-23, originally discovered due to their ability of inducing bone formation and cartilage. BMPs are pivotal in building a group of morphogenetic signals orchestrating tissue architecture throughout the body (7). Recent research shows that the highest concentration of BMPs is in articular cartilage, osteoblasts, osteoclasts and osteoprogenitor cells (8,9). BMP-4 is essential for the skeletal development during embryogenesis and its expression increases in adulthood during fracture healing. At the molecular level, specific genetic variants of BMP4 are associated with the risk of decreased bone density of the hip in postmenopausal women (10).

FGF and their receptors (FGFRs) play important roles in

morphogenesis and organogenesis by controlling the levels of cell proliferation, differentiation, migration, adhesion and death (11).

The combination of angiogenic and osteogenic growth factors such as BMP/TGF- β and BMP/FGF is able to promote bone regeneration by enhancing osseointegration *in vivo*. The antagonism between BMP and FGF contributes to healing in bone lesions. FGFR-1 is a positive regulator of bone formation and interacts with FGF3 and FGF10 promoting angiogenesis and fracture healing (12,13).

The variation in severity during peri-implantitis development, observed among volunteers that underwent similar environmental factors, suggests that the genetic aspects of peri-implantitis need to be investigated to understand the regulation in the pathogenesis associated with this disease (3). Therefore, considering the interaction and modulation of the BMP/FGF axis during bone remodeling, the study hypothesis was that the process of peri-implantitis may be related to genetic alterations in the BMP and FGF families. Thus, the aim of this study was to analyze the correlation between genetic polymorphisms in BMP4, FGF3, FGF10 and FGFR1 and the bone loss process around dental implant.

Material and Methods

Volunteers

This is an observational, cross-sectional and double-blinded study. Two hundred and fifteen volunteers, with 754 dental implants, were enrolled for the study from the pool of the patients attended at the Dental Implantology Clinic of the School of Dentistry at UFF, Brazil, over a course of one year. The clinical procedures were conducted in accordance with the recommendations of the local Research Ethics Committee (Registration number 238/10). The term of informed consent was obtained from all participants. The initial clinical parameters of the volunteers are in Table 1. All participants provided their medical and dental history (Table 2) and reported smoking habits. The exclusion criterion was implant failure (pathologic bone loss, implant mobility or implant loss) before the osseointegration period (3 months for mandible and six months for maxillary), bisphosphonate use, pregnancy and/or lactation in female volunteers, no preoperative radiography, one stage or immediate implant placement, concurrent bone grafting required, early implant exposure during osseointegration period, non-treated periodontitis and non-compliance with study protocol. The inclusion criteria were as follows: at least one osseointegrated endosseous implant, immediate postoperative radiography showing the vertical bone level around implant to compare bone level after the osseointegration period, periapical radiography showing periodontal status before implant placement, and annual follow-up clinical and radiographic examinations. All implants were placed in a submerged healing modality (two-stage concept) in sites that had previously showed favorable bone quality and quantity (14).

Diagnosis of Peri-implantitis

Peri-implant sites were submitted to clinical examination based on Junior et al. (14), which consisted of visual inspection and palpation, analysis of mucosa inflammation, probing pocket depth, bleeding on probing and spontaneous bleeding in four aspects (mesial, buccal, distal and lingual/palatine), presence of plaque, peri-implant phenotype, implant mobility (any mobility during percussion test), osseointegration period and implant platform type. Conventional periapical radiography, using the paralleling technique, was used to assess the presence of vertical bone loss around the implants by measuring the height of peri-implant bone and comparing it with the initial radiography taken immediately after implant placement. According to the clinical and radiographic characteristics of the peri-implant sites, volunteers were characterized as having healthy sites - no clinical signs of inflammation in the peri-implant mucosa and no signs of bone loss – or peri-implantitis with radiographic signs of pathologic bone loss in at least one region. Physiological bone loss was characterized considering a normal bone loss of 1 mm during the first year following implant placement and 0.2 mm for subsequent years. The diagnosis of peri-implantitis was based on radiographic bone level. If the total bone loss was higher than 1 mm and 0.2 mm per year, the volunteer was diagnosed with peri-implantitis.

Selection of Single Nucleotide Polymorphism (SNP) and Genotyping

DNA from all participants was extracted from buccal cells after vigorously rinsing with 5 mL of saline solution for 60 s, as described previously (15). A NanoDrop spectrophotometer (Thermo Scientific, Wilmington, DE, USA) was used to determine the amount and purity of the DNA. Only DNA samples showing A260 nm/A280 nm ratios greater than 1.9 were used. All procedures included in SNP selection and analysis followed the STREGA reporting recommendations (16). Linkage disequilibrium relationships and gene structure were considered to select the thirteen SNPs in the candidate's genes included in this study. The least allele frequencies reported in the database of the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/ SNP/) was >0.2 (Table 4).

Real-time polymerase chain reaction using the TaqMan method (Applied Biosystems, Foster City, CA, USA), maintaining a total of 1,5-μL reaction, was used to genotype the regions selected in the thermal cycler PTC-

225 (Peltier Thermal Cycler, Bio Rad Life Science, Corston, UK). As BMP4, FGF3 and FGF10 genes are found in the same chromosome, it is believed that they may act as a unit. Therefore, polymorphisms in these genes were not analyzed individually but in combination, termed as haplotype.

Statistical Analysis

The nominal variables were expressed as frequencies and percentages. The chi-square was used to access the significance of the nominal variables among the groups. Continuous variables were expressed as mean and standard deviation. After the Shapiro-Wilk test showed normal distribution, analysis of variance and the Student's t-test were applied. Differences in the frequency of genotypes and alleles between peri-implantitis and the control groups were analyzed using Fisher's exact test and chi-square test, after fitting in Hardy-Weinberg equilibrium. The p values of <0.05 were considered statistically significant, and the risk of individual alleles and genotypes associated with the development of the disease was calculated by odds ratio (OR) in a 95% confidence interval. Multivariate regression analysis was used to explore many covariates simultaneously. Statistical analysis was applied using STATA 11.1 (Stata Corp, College Station, TX, USA). To calculate the haplotypes was used the computer program ARLEQUIN (v.20-ttp://anthro.unige.ch/arlequin).

Results

Among all 215 volunteers evaluated over the course of one year, 148 (69%) were women and 67 (31%) men, with mean age 55.12±12.63 years. No difference was found between the test group (peri-implantitis) when compared with the control group (healthy) regarding the ethnicity, gender, age and smoking habit (Table 1).

Total edentulism (p<0.0001) and thin peri-implant phenotype (p=0.04) were highly incident in volunteers with peri-implantitis (Table 2). The peri-implant status (Table 3) showed a high prevalence for bleeding on probing, spontaneous bleeding, high probing pocket depth, presence of plaque and implant mobility in peri-implantitis volunteers (p<0.001 for all).

The polymorphic genotype TT of BMP4 rs2761884 was associated with the healthy group (p=0.01). FGF3 rs4631909 TT+CT genotypes also showed association with the control group (p=0.04) (Table 5). In addition, the frequency of C allele for FGF3 rs4631909 showed a tendency for association with the peri-implantitis group (p=0.08) (Table 6). Genotype distributions were within Hardy-Weinberg equilibrium.

Haplotypes distribution in both groups (Table 7). The distribution of haplotypes arranged as alleles was constructed for BMP4, FGF3 and FGF10 genes and assessed for association. A significant association between FGF10 CCTG haplotype and peri-implantitis was evident (p=0.03). There also was a significant association between the GAAA (p=0.05) and GGGA (p=0.02) haplotypes of the BMP4 gene and occurrence of peri-implantitis. FGF3 TGCG haplotype showed a tendency for association with peri-implantitis.

In order to assess risk factors concurrently, a multivariate logistic regression of individual parameters in the test groups was performed (Table 8). This yielded adjusted odds ratios (OR) for individual parameters, including age, gender, BMP4 rs2761884 and FGF3 rs4631909, previously associated with protection against peri-implantitis. This analysis confirmed previous univariate results.

Discussion

Evidence shows that peri-implant diseases are related to genetic factors (17). Considering the interaction and modulation of the BMP/FGF axis during bone remodeling, the study aimed to analyze the correlation between BMP4, FGF3, FGF10 and FGFR1 genes in the pathological process of peri-implant bone loss. To elucidate such association, this study was conducted to evaluate a total of 215 volunteers divided into two groups, according to the presence or absence of peri-implantitis. This study confirmed the association of BMP4, FGF3 and FGF10 haplotypes with peri-implantitis, irrespective of the presence of previously described risk factors, suggesting that different pathways can trigger this disease.

Peri-implantitis affects a group of subjects and it is correlated to risk factors that have been pre-established in the literature, such as smoking,

Table 1. Baseline characteristics of the complete sample

Characteristic	Total [N=215; n (%)]	Control [N=129; n (%)]	Peri-implantitis [N=86; n (%)]	p-value	Odds ratio (CI)
Ethnic group					
Whites	189 (88.0)	112 (86.82)	77 (89.53)	0.55	1.30 (0.51-3.34)
Non-Whites	26 (12.0)	17 (13.17)	9 (10.46)		
Age (years)	55.12 ± 12.63	53.27 ±13.18	57.89 ±11.29	0.99	----
Sex					
Female	148 (68.8)	86 (66.67)	62 (72.09)	0.40	1.29 (0.68-2.45)
Male	67 (31.2)	43 (33.33)	24 (27.90)		
Smoking					
Non-smoker	194 (90.2)	116 (89.92)	78 (90.70)	0.85	0.92 (0.33-2.50)
Smoker	21 (9.8)	13 (10.07)	8 (9.30)		

Table 2. Clinical findings and anamnesis data of the discovery sample

Parameters	Healthy [N=129; n (%)]	Peri-implantitis [N=86; n (%)]	p value	Odds ratio (CI)
General medical condition				
Diabetes	2 (1.56)	5 (5.81)	0.08	3.92 (0.65-29.94)
Rheumatoid diseases	4 (3.12)	3 (3.48)	0.87	1.13 (0.19-6.17)
Osteoporosis	2 (1.56)	0 (0)	0.24	0.00 (0.00-6.14)
Hypotireoidism	6 (4.65)	2 (2.32)	0.37	0.49 (0.07-2.76)
Antimicrobials	0	0 (0)	---	---
NSAIDs†	1 (0.78)	0 (0)	0.41	---
SAIDs‡	0	2 (2.32)	0.08	RR 2.54 (2.15-2.99)
Hormone reposition	4 (3.12)	3 (3.48)	0.87	1.13 (0.19-6.17)
Antidepressant	4 (3.12)	3 (3.48)	0.87	1.13 (0.19-6.17)
Clinical measurements				
Edentulism				
Total	24 (18.60)	69 (80.23)	<0.0001	18.69 (8.79-40.34)
Partial	104 (80.62)	16 (18.60)		
Periodontal phenotype				
Thin#	48 (37.20)	44 (51,16)	0.04	1.77 (0.98-3.20)
Thick	79 (61.24)	41 (47.67)		

NSAIDs: Nonsteroidal anti-inflammatory drugs. SAIDs: Steroidal anti-inflammatory drugs.

Table 3. Peri-implant status of the volunteers

Peri-implant status	Healthy [N=129; n (%)]	Peri-implantitis [N=86; n (%)]	p value	Odds ratio (CI)
Bleeding on probing	19 (14.73)	52 (60.46)	<0.001	8.55 (4.41-17.96)
Spontaneous bleeding	0 (0.0)	11 (12.79)	<0.001	RR 2.72 (2.27-3.26)
Probing pocket depth (mm)	1.86±0.99	2.46±1.26	<0.001	------
Plaque index	11 (8.52)	22 (25.58)	<0.001	3.69 (1.58-8.72)
Peri-implant phenotype				
Thin	50 (38.75)	43 (50,00)	0.07	1.65 (0.91-2.99)
Thick	79 (61.25)	43 (50.00)		
Mobility (absence/ presence)	0	8 (9.30)	<0.001	RR 2.65 (2.23-3.16)
Implant-platform type				
External Hexagon	66 (51.16)	50 (58.13)	0.43	
Internal Hexagon	10 (7.75)	8 (9.30)		
Morse Cone	50 (38.76)	27 (31.39)		
Others	5 (3.87)	1 (1.16)		
Implant region				
Superior	63 (48.83)	43 (50.00)	0.78	0.93 (0.52-1.66)
Inferior	68 (52.71)	43 (50.00)		
Osseointegration period (months)	33.95±31.07	35.85±37.42	0.70	---

poor oral hygiene, diabetes and history of periodontal diseases (18). Therefore, with the purpose of better understanding the correlation between risk factors and the development of peri-implantitis, this study included smokers and subjects with systemic disease, showing that there is a correlation between diabetes with the development of peri-implantitis. However, it was not evident that smoking is a possible risk indicator for peri-implantitis, which may indicate that other non-described factors may trigger peri-implant bone loss.

Although no studies in the literature discuss the importance of the correlation between BMP and FGF in implant dentistry, the whole process of bone formation, bone repair and homeostasis is widely mediated by these soluble factors associated with their receptors (19).

In an endeavor to elucidate the relationship between the genetic factor and peri-implantitis, genotypes and allele frequencies in specific regions in BMP4, FGF3, FGF10 and FGFR1 genes were evaluated using the data from the International HapMap Project (20). The results of the single marker showed that BMP4 rs2761884 (G>T) and FGF3 rs4631909 (C>T) substitutions were associated with absence of peri-implantitis and there seems to be no major influence of the other gene encoding mediator in bone remodeling. However, when different regions in the same gene were analyzed together, in an endeavor to understand the effect of the different regions responsible for the expression of the gene, an association among GGGA and GAAA BMP4, TGCG FGF3 and CCTG FGF10 haplotypes with pathologic peri-implant bone loss was clearly observed.

The study of Ren et al. (21) found that BMP4 TGGGCTT haplotype was associated with the overexpression of BMP4 mRNA in subjects with ossification of the posterior longitudinal ligament. Guimaraes et al. (8) analyzed multiple variants in the BMP4 gene and believe that the BMP4 haplotype may trigger the exacerbated expression of BMP4, interfering in bone homeostasis and causing the non-union of fractures.

The antagonism between BMP and FGF contributes to the repair of bone lesions. FGF/FGFR signaling is present in endochondral and intramembranous bones and plays important roles in regulating their development and growth (22). In the present study, it is clear that individuals carrying CC genotype for FGF3 rs4631909 have increased risk of peri-implantitis, in contrast to the TT genotype, which acts as a protective factor even when analyzed together with other areas of the same chromosome. Furthermore, it is important to consider that FGFR1 is a positive regulator for bone formation: it has a synergistic effect with FGFR2 and stimulates osteoblastic differentiation (23). FGFR1 and FGFR2 are important in regulating the morphology and patent of craniofacial sutures (24). However, in this study, FGFR1 rs13317 was not associated with peri-implantitis. It is possible that the variant of FGFR1 favors adequate bone repair.

In summary, evidence was obtained for the association among the BMP4, FGF3 and FGF10 haplotypes with peri-implantitis. However, further studies are required (larger samples with different populations, greater knowledge of the genes involved in bone destruction around implants) to confirm these findings and to identify other genes responsible for the susceptibility to the development

Table 4. Characteristics of genetic markers

Gene	SNP ID	Chromosome	SNP Type	Base change*	MAF**
BMP4	rs2761884	Ch14	intron	G>T	0.366
	rs17563	Ch14	exon	C>T	0.371
	rs2071047	Ch14	intron	A>G	0.401
	rs762642	Ch14	intron	A>C	0.352
FGF3	rs7932320	Ch11	intron	C>T	0.486
	rs1893047	Ch11	intron	A>G	0.428
	rs4631909	Ch11	intergenic	C>T	0.478
	rs4980700	Ch11	intergenic	A>G	0.439
FGF10	rs1448037	Ch5	intron	C>T	0.361
	rs900379	Ch5	intron	C>T	0.483
	rs1011814	Ch5	intron	C>T	0.485
	rs593307	Ch5	intron	A>G	0.364
FGFR1	rs13317	Ch8	3`UTR	C>T	0.275

*Base change according to Applied Biosystem; **MAF: minor allele frequency according to GenBank; Base change in BMP4 rs 17563 had as reference the Esembl.

Table 5. Genotype frequencies of the SNPs in all volunteers

Gene	SNP	Genotypes	Healthy [N=129; n (%)]	Peri-implantitis [N=86; n (%)]	p value*
BMP4	rs2761884	GG	48 (37.20)	36 (41.86)	
		GT	55 (42.64)	41 (47.67)	0.01
		TT	23 (17.83)	4 (4.65)	
		GT+TT	78 (60.46)	45 (52.32)	0.36
	rs17563	AA	27 (20.93)	22 (25.58)	
		AG	64 (49.61)	40 (46.51)	0.63
		GG	34 (26.36)	19 (22.09)	
		AG+GG	59 (45.73)	98 (113.95)	0.55
	rs2071047	AA	19 (14.73)	9 (10.46)	
		AG	48 (37.21)	44 (51.16)	0.15
		GG	50 (38.76)	27 (31.39)	
		AG+GG	69 (53.49)	36 (41.86)	0.32
	rs762642	AA	105 (81.39)	72 (83.72)	
		AC	18 (13.95)	9 (10.46)	0.46
		CC	0	0	
		AC+CC	18 (13.95)	9 (10.46)	---
FGF-3	rs7932320	CC	24 (18.60)	18 (20.93)	
		CT	51 (39.53)	38 (44.18)	0.47
		TT	52 (40.31)	27 (31.39)	
		CT+TT	103 (79.84)	65 (75.58)	0.62
	rs1893047	AA	39 (30.23)	18 (20.93)	
		AG	56 (43.41)	40 (46.51)	0.27
		GG	31 (24.03)	26 (30.23)	
		AG+GG	87 (67.44)	66 (76.74)	0.12
	rs4631909	CC	20 (15.50)	23 (26.74)	
		CT	56 (43.41)	38 (44.18)	0.05
		TT	53 (41.08)	24 (27.90)	
		CT+TT	109 (84.49)	62 (72.09)	0.04
	rs4980700	AA	43 (33.33)	19 (22.09)	
		AG	56 (43.41)	37 (43.02)	0.25
		GG	29 (22.48)	24 (27.90)	
		AG+GG	85 (65.89)	61 (70.93)	0.13
FGF-10	rs1448037	CC	46 (35.65)	37 (43.02)	
		CT	61 (47.28)	36 (41.86)	0.32
		TT	21 (16.28)	9 (10.46)	
		CT+TT	67 (51.93)	46 (53.48)	0.59
	rs900379	CC	30 (23.25)	24 (27.90)	
		CT	63 (48.84)	33 (38.37)	0.36
		TT	35 (21.13)	27 (31.39)	
		CT+TT	98 (75.97)	60 (69.76)	0.4
	rs1011814	CC	36 (27.90)	26 (30.23)	
		CT	61 (47.28)	34 (39.53)	0.73
		TT	29 (22.48)	19 (22.09)	
		CT+TT	90 (67.77)	53 (61.62)	0.51
	rs593307	AA	24 (18.60)	12 (13.95)	
		AG	59 (45.73)	32 (37.20)	0.29
		GG	39 (30.23)	33 (38.37)	
		AG+GG	63 (48.83)	45 (52.32)	0.35
FGFR1	rs13317	CC	5 (3.87)	5 (5.81)	
		CT	39 (30.23)	35 (40.70)	0.13
		TT	83 (64.34)	42 (48.83)	
		CT+TT	122 (94.57)	77 (89.53)	0.48

Table 6. Allele distribution between groups

Gene	SNP ID	A1	MAF Control	MAF Test	p value	Odds ratio	95% CI
BMP4	rs2761884	T	0.40	0.30	0.13	1.56	0.83-2.92
	rs17563	A	0.47	0.52	0.47	0.82	0.45-1.48
	rs2071047	A	0.37	0.39	0.77	1.09	0.59-2.01
	rs762642	C	0.07	0.06	0.77	0.85	0.24-2.94
FGF3	rs7932320	C	0.39	0.45	0.39	1.28	0.70-2.34
	rs1893047	A	0.53	0.45	0.25	0.73	0.40-1.31
	rs4631909	C	0.37	0.49	0.08	1.64	0.90-2.99
	rs4980700	G	0.45	0.53	0.25	1.38	0.76-2.50
FGF10	rs1448037	T	0.40	0.33	0.63	0.87	0.46-1.63
	rs900379	T	0.47	0.46	0.89	0.96	0.54-1.70
	rs1011814	C	0.47	0.51	0.57	1.17	0.65-2.12
	rs593307	A	0.44	0.36	0.24	0.72	0.39-1.31
FGFR1	rs13317	C	0.19	0.27	0.17	1.58	0.77-3.24

A1: Minor allele (based on whole sample)/ MAF_C: minor allele frequency in control/ MAF_T: minor allele frequency in test. *p calculated by chi-square test. p-values <0.05 are considered significant

Table 7. Haplotypes distributions in all groups

Gene	Haplotype	Frequency estimation		p value	Odds Ratio	95% CI
		Healthy [N=129; n (%)]	Peri-implantitis [N=86; n (%)]			
BMP4 (rs2761884; rs17563; rs2071047; rs762642)	TGGA	0.36	0.25	---	1.00	---
	GAAA	0.29	0.32	0.05	0.57	0.32-1.01
	GGGA	0.15	0.22	0.02	0.48	0.25-0.91
	GAGA	0.07	0.09	0.11	0.52	0.23-1.15
	GAAC	0.05	0.04	0.81	1.14	0.41-3.11
	TAGA	0.03	0.03	0.58	0.72	0.22-2.36
FGF3 (rs7932320; rs1893047; rs4631909; rs4980700)	TATA	0.52	0.43	---	1.00	---
	CGCG	0.30	0.36	0.11	0.71	0.46-1.08
	TGCG	0.05	0.10	0.05	0.48	0.23-1.01
	CGTG	0.07	0.04	0.58	1.28	0.54-3.04
	TGTA	0.01	0.01	0.93	1.09	0.15-8.02
FGF10 (rs1448037; rs900379; rs1011814; rs593307)	CTCG	0.50	0.49	---	1.00	---
	TCTA	0.39	0.31	0.33	1.24	0.81-1.89
	CCTG	0.05	0.13	0.03	0.46	0.23-0.94
	CTCA	0.01	0.01	0.73	1.43	0.19-10.91
	CCTA	0.01	0.01	0.98	0.96	0.08-11.09

*p-values <0.05 are considered significant.

Table 8. Multinominal logistic regression results for the diseased groups (reference = peri-implantitis group)

Parameters	Z	p-value	Odds Ratio	95% CI
Age	-2.58	0.01	0.96	0.94-0.99
BMP4 rs2761884				
GG	---	1.0	---	---
GT	0.36	0.71	1.11	0.60-2.06
TT	2.61	0.009	4.40	1.44-13.43
FGF3				
CG	---	1.0	---	---
CT	1.45	0.14	1.75	0.82-3.75
TT	2.67	0.008	3.02	1.34-6.83

of peri-implantitis, and thus provide new approaches to molecular-level investigations when treating these volunteers, increasing the rate of success in implant rehabilitation.

Resumo

Apesar do alto índice de sucesso em implantodontia, falhas tem aumentado drasticamente, estando associadas ao desenvolvimento de peri-implantite. A perda óssea peri-implantar é influenciada por múltiplos fatores, incluindo causas genéticas e ambientais. As BMPs (proteínas ósseas morfogenéticas) são fatores de crescimento indutores da formação óssea. Os FGFs (fatores de crescimento dos fibroblastos) e seus receptores (FGFRs) desenvolvem importante função na proliferação, diferenciação e migração celular. A relação BMP/FGF é responsável pela regeneração e perda óssea. O objetivo deste estudo foi estudar a possível correlação entre os genes BMP4, FGF3, FGF10 e FGFR1 e a perda óssea peri-implantar. Duzentos e quinze voluntários, com 754 implantes, foram submetidos ao exame oral e divididos em grupo saúde (n=129) e peri-implantite (n=86). Treze polimorfismos nos genes BMP4, FGF3, FGF10 e FGFR1 foram analisados individualmente e como haplótipos. O teste do qui-quadrado correlacionou as frequências dos genótipos, alelos e haplótipos. Valores de p<0,05 foram considerados estatisticamente significantes. Voluntários com peri-implantite mostraram alta incidência de edentulismo total (p<0,0001) e biotipo periodontal fino (p<0,04). Sangramento espontâneo, placa e mobilidade do implante foram altamente incidentes no grupo peri-implantite (p<0,0001). O genótipo polimórfico TT para BMP4 rs2761884 foi associado com saúde peri-implantar (p=0,01). FGF3 rs4631909 (genótipos TT+CT) mostraram associação com o grupo controle (p=0,04). A frequência do alelo C para FGF3 rs4631909 mostrou uma tendência de associação com peri-implantite (p=0,08). Os haplótipos FGF10 CCTG (p=0,03), BMP4 GAAA (p=0,05) e GGGA (p=0,02) foram associados com peri-implantite (p=0,03). Sendo assim, conclui-se que os haplótipos BMP4 e FGF10 estão associados com peri-implantite.

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