CLAUDIA CRISTINA MONTES

Análise da Associação dos Polimorfismos *IL1B* (C+3954T) e *IL1RN* (intron 2) com a Perda de Implantes Dentais Osseointegráveis

CURITIBA

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Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde (PPGCS) do Centro de Ciências Biológicas e da Saúde (CCBS) da Pontifícia Universidade Católica do Paraná (PUCPR), como parte dos requisitos para a obtenção do título de Doutor em Ciências da Saúde, Área de Concentração Medicina.

Orientadora: Profa. Dra. Paula Cristina Trevilatto

CURITIBA

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Dedicatória

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TEMPO CERTO

De uma coisa podemos ter certeza:
De nada adianta querer apressar as coisas;
tudo vem ao seu tempo,
dentro do prazo que lhe foi previsto,
mas a natureza humana não é muito paciente.
Temos pressa em tudo,
aí acontecem os atropelos do destino,
aquela situação que você mesmo provoca
por pura ansiedade de não aguardar
o Tempo Certo.
Mas alguém poderia dizer:
Mas qual é esse tempo certo???
Bom, basta observar os sinais...
Quando alguma coisa está para acontecer
ou chegar até sua vida,
pequenas manifestações do cotidiano,
enviarão sinais indicando
o caminho certo.
Pode ser a palavra de um Amigo,
um texto lido, uma observação qualquer;
mas com certeza,
o sincronismo se encarregará de colocar você
no lugar certo, na hora certa, no momento certo,
diante da situação ou da pessoa certa!!!
Basta você acreditar que
Nada Acontece Por Acaso!!!
E talvez seja por isso que você esteja agora lendo
essas linhas...
Tente observar melhor o que está a sua volta.
Com certeza alguns desses sinais já estão por perto,
e você nem os notou ainda.
Lembre-se que:
O universo sempre conspira a seu favor,
quando você possui um objetivo claro
e uma disponibilidade de crescimento.

Paulo Coelho

SUMÁRIO

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RESUMO

Resumo Os implantes dentais osseointegráveis são considerados a melhor opção para o tratamento da perda dental. Apesar do alto índice de sucesso, estudos demonstram que falhas podem ocorrer. As falhas dos implantes podem estar relacionadas à incapacidade do hospedeiro em estabelecer ou manter a osseointegração. O fenômeno de *clusterização*, no qual alguns pacientes sofrem múltiplas perdas, sugere que características individuais têm um papel importante na falha da osseointegração. Entretanto, pouco se sabe sobre a influência genética na susceptibilidade à perda de implantes dentais osseointegráveis. Os objetivos deste estudo foram: i) identificar fatores clínicos que levaram à perda de implantes dentais em pacientes tratados no Instituto Latino Americano de Pesquisa e Ensino em Odontologia (ILAPEO); ii) investigar a associação entre os polimorfismos em genes dos mediadores inflamatórios *IL1B* (+3954) e *IL1RN* (íntron 2) e a perda de implantes dentais osseointegráveis. Foi realizada uma análise retrospectiva em todos os 3.578 prontuários de pacientes atendidos no ILAPEO, no período de 1996 a 2006, juntamente com radiografias panorâmicas e periapicais. A perda de implantes ocorreu em 3,5% (126/3.578) dos pacientes. Homens apresentaram um maior número de implantes perdidos. Foram detectadas as principais causas de perda de implantes, sendo que 75% das perdas não apresentaram causa clínica aparente. A perda de implantes ocorreu preferencialmente em região posterior de mandíbula. Posteriormente, foram selecionados 266 pacientes divididos em: *Grupo Controle (C)*, 176 indivíduos com pelo menos um implante em função por no mínimo seis meses e sem nenhuma perda e *Grupo Teste (T)*, 90 indivíduos com perda de ao menos um implante. O perfil socioeconômico, estado médico geral, parâmetros de higiene bucal e aspectos clínicos, como número de dentes presentes e a condição periodontal, foram avaliados. O DNA obtido a partir de células epiteliais da mucosa jugal foi amplificado pela técnica de reação em cadeia da polimerase (PCR). Os polimorfismos estudados apresentaram-se em equilíbrio de Hardy-Weinberg. Os resultados obtidos neste estudo sugerem que os parâmetros clínicos: edentulismo, profundidade de bolsa e número de dentes presentes estejam relacionados à perda de implantes dentais osseointegráveis. Os polimorfismos *IL1B* (+3954) e *IL1RN* (intron 2) não estiveram associados com a perda de implantes dentais osseointegráveis na população estudada. Observou-se que aspectos clínicos, mas não os polimorfismos genéticos investigados, estiveram associados à perda de implantes dentais osseointegráveis.

ABSTRACT

Abstract Dental implants have become an important therapeutical modality for tooth replacement. Although the high success rate showed in longitudinal studies, failures occur, even in patients who present appropriate clinical conditions. Together with the clusterization phenomenon, which is the presence of multiple implant losses in the same group of individuals, this fact suggests that host response aspects can influence the implant failure process. However, little is known about the influence of genetic susceptibility on implant loss. The aims of the present study were: i) identify clinical factors related to dental implant loss in patients from the Latin American Dental Research Institute (ILAPEO); ii) investigate the association between dental implant loss and the functional polymorphisms *IL1B* (+3954) *and IL1RN* (intron 2). In a retrospective analysis of 3,578 records, panoramic and periapical radiographs of patients who had placed implants in ILAPEO during the period of 1996 to 2006 were analyzed. Implant loss occurred in 126 (3.5%) patients. Men lost more implants than women. The main clinical detectable causes of implant loss were evaluated. Failure was more frequent when the implant was installed in the posterior jaw. Most implant failure (75%) did not present apparent clinical cause. A sample of 266 patients was selected and divided in: *Test group (T)* - 90 subjects with implant loss, and *Control group (C)* - 176 subjects with at least one implant in function for at least six months. Patients' socioeconomic profile, general medical condition, hygiene parameters, and clinical measurements such as number of teeth and periodontal status, were analyzed. Genomic DNA from oral mucosa was amplified by polymerase chain reaction (PCR). The fragments were submitted to agarose gel electrophoresis, followed by ethidium-bromide staining method. Polymorphisms *IL1B* (+3954) and *IL1RN* (intron 2) were in Hardy-Weinberg equilibrium. Regarding clinical aspects, the following parameters were observed to influence implant failure: edentulism, probing pocket depth, and number of present teeth. No differences in genotype distribution and allele frequencies between C and T groups were found for *IL1B* (+3954) and *IL1RN* (intron 2) polymorphisms in the study population. It was observed that clinical aspects, but not the study polymorphisms, were associated with osseointegrated dental implant loss.

INTRODUÇÃO

1. Introdução

1.1 Implantes dentais osseointegráveis

Os implantes dentais tornaram-se uma importante modalidade terapêutica nas últimas décadas (Att & Stappert 2003; Henry 2005), principalmente após os trabalhos desenvolvidos por Brånemark (Albrektsson et al. 1986; Smith & Zarb 1989).

Apesar do número reduzido de insucessos (Adell et al. 1990; Lekholm et al. 1999; Esposito et al. 2004a; Scolozzi & Jaques 2004), mesmo seguidas as recomendações e indicações clínicas precisas, podem ocorrer perdas de implantes (Ellen 1998; Goodacre et al. 1999; Graziani et al. 2004; Fugazzotto 2005). A perda de implantes pode ser dividida em precoce, na qual não ocorre a osseointegração, e tardia, na qual a osseointegração ocorreu, mas não pôde ser mantida, após um período do implante em função (Esposito et al. 1998a; Esposito et al. 2004b). O sucesso da colocação do implante depende de vários fatores, tais como: biomaterial e propriedades de superfície do implante (topografia e rugosidade) (Haraldson 1980; Albrektsson et al. 1981; Albrektsson 1983; Carlsson et al. 1986), ausência de complicações cirúrgicas, como a ocorrência de superaquecimento ósseo e contaminação (Lavelle et al. 1981; Eriksson & Albrektsson 1983; Eriksson & Albrektsson 1984; van Steenberghe & Quirynen 1990; Kuttenberger et al. 2005), volume e qualidade óssea (Esposito et al. 1998b; Stanford 2003; Rosenberg et al. 2004; Degidi & Piattelli 2005), ausência de sobrecarga oclusal (Albrektsson et al. 1981; Misch et al. 2004) e periimplantite (Smith & Zarb 1989; Rosenberg et al. 2004). Além da perda de implantes, a reabsorção óssea marginal ao redor dos implantes tem sido também considerada fator de insucesso (Shimpuku et al. 2003).

As causas biológicas da falha de implantes podem estar relacionadas a aspectos da resposta imuno-inflamatória do hospedeiro (Esposito et al. 1998a). Um processo inflamatório intenso (Kao et al. 1995) dificulta a osseointegração (Scaglioni & Deliga 1996) e pode resultar clinicamente na perda do implante. Falhas no processo da osseointegração constituem uma das situações mais delicadas na implantodontia (Bianchi et al. 2003).

A resposta inflamatória envolve inúmeras interações complexas entre macrófagos, linfócitos e outras células do sistema imunológico. Estas interações são mediadas por polipeptídeos de pequena massa molecular, conhecidos como citocinas (Abbas et al. 1998). O grupo das citocinas inclui as interleucinas (IL) que podem atuar na modulação da degradação dos componentes da matriz extracelular e na reabsorção óssea (Birkedal-Hansen 1993). A lesão cirúrgica, em decorrência da inserção do implante, desencadeia uma resposta inflamatória aguda, na qual inúmeras citocinas e fatores de crescimento servem de mediadores, que podem promover regeneração ou reparo. Nesta etapa, níveis elevados de citocinas pró-inflamatórias com atividade de reabsorção óssea, como a interleucina-1 (IL-1), podem proporcionar a indesejável reabsorção óssea marginal ao redor dos implantes, acarretando prejuízos funcionais e estéticos, ou prejudicar o estabelecimento da osseointegração, resultando na perda do implante.

A ocorrência de insucesso na colocação de implantes dentais não parece estar distribuída de forma aleatória na população, ou seja, há um pequeno grupo de indivíduos no qual ocorrem inúmeras perdas (Tonetti 1999). A observação de que indivíduos com um implante falho são mais propensos a sofrer outras falhas (Weyant & Burt 1993; Hutton et al. 1995) pode indicar a existência de grupos de risco para a perda de implantes, sugerindo que fatores

sistêmicos ou genéticos podem estar envolvidos nesses insucessos (Esposito et al. 1998a).

Os critérios para a avaliação do fracasso de um implante estão baseados em alterações clínicas e radiográficas, que normalmente refletem condições patológicas extensas (Kao et al. 1995). A identificação de fatores relacionados ou determinantes da perda de implantes pode permitir uma intervenção precoce, minimizando as lesões aos tecidos e aumentando o potencial de sucesso terapêutico (Eley et al. 1991; Kao et al. 1995).

1.2 A interleucina-1 como mediador inflamatório

Estudos têm demonstrado que o material de revestimento dos implantes, considerado inócuo, pode estimular células imunogênicas a produzir mediadores inflamatórios *in vitro* (Perala et al. 1992; Harada et al. 1996). As interleucinas são mediadores-chave do processo inflamatório (Genco 1992).

A atividade pró-inflamatória da IL-1 é exercida por dois tipos de polipeptídeos: IL-1*α* e IL-1*β*. As duas formas de IL-1 mostram menos de 30% de homologia estrutural; porém as duas ligam-se aos mesmos receptores de superfície e suas atividades biológicas são essencialmente idênticas (Abbas et al. 1998). A IL-1*α* parece se concentrar na membrana celular, enquanto a IL-1*β* é secretada para o meio extracelular e parece ser a principal responsável pelas atividades da IL-1 (Dinarello 1988). A família da IL-1 ainda é constituída por um terceiro polipeptídeo, denominado antagonista do receptor da IL-1 (IL-1ra). Esta citocina funciona como um inibidor competitivo, pois se liga aos receptores da IL-1 inibindo a sua atividade biológica (Abbas et al. 1998).

A IL-1 é responsável por sinalizar a invasão de microrganismos agressores e estimular respostas que favorecem sua eliminação. Porém, quando seus níveis estão elevados, pode contribuir para o desenvolvimento de processos patológicos. A IL-1 é considerada citocina pró-inflamatória com importância central na iniciação e manutenção das respostas inflamatórias agudas (Sim 1993). Além de atuar como mediadora da inflamação local, a IL-1 pode apresentar efeitos sistêmicos (Dinarello 1988). No sítio da inflamação, atua sobre macrófagos, aumentando ainda mais a produção de IL-1. Nas células endoteliais, aumenta a expressão de moléculas de superfície que medeiam à adesão leucocitária (Abbas et al. 1998). Essa citocina atua ainda sobre fibroblastos, estimulando sua proliferação e a transcrição de colágeno tipo I, III e IV. Dessa forma, o desenvolvimento de fibrose parece ser em parte mediado pela IL-1 (Dinarello 1988). A IL-1 também possui efeitos significativos no tecido ósseo. Estudos *in vitro* e *in vivo* indicam que esta citocina desempenha potente atividade na reabsorção óssea (Meikle et al. 1990). Osteoblastos possuem receptores de superfície para a IL-1 que, quando ativados, estimulam a produção de prostaglandina e da própria IL-1, além de modular a expressão gênica de diversas outras citocinas. Dessa forma, sugere-se que a IL-1 participa da patogênese de doenças que envolvem o tecido ósseo (Masada et al. 1990; Tatakis 1993).

Foram observados níveis elevados de IL-1 no fluido gengival (Masada et al. 1990; Preiss & Meyle 1994; Tsai et al. 1995) e nos tecidos gengivais (Stashenko et al. 1991; McGee et al. 1998) de pacientes com periodontite, sugerindo que a produção local desta interleucina contribui para a destruição de tecidos periodontais. A IL-1β parece também participar da destruição tecidual durante o processo de periimplantite. Implantes com sinais de

inflamação tecidual apresentam níveis elevados de IL-1β no fluido gengival quando comparados a sítios com implantes saudáveis (Kao et al. 1995; Panagakos et al. 1996; Curtis et al. 1997; Aboyoussef et al. 1998). Estudos concluíram que níveis de IL-1β parecem ser mais relevantes no indivíduo que no sítio do implante, e sugerem que em indivíduos com periimplantite, os implantes saudáveis apresentam um maior risco de futuras falhas (Salcetti et al. 1997). Níveis elevados de IL-1β também foram observados em implantes clinicamente saudáveis, que posteriormente fracassaram (Curtis et al. 1997), sugerindo que o monitoramento das concentrações da IL-1β poderia auxiliar no diagnóstico precoce de doença ativa ao redor de implantes. Estudos recentes têm sugerido que a presença de elevados níveis de IL-1β no fluido gengival pode ser utilizada como efetivo marcador biológico para monitorar, de forma objetiva, a condição de saúde do implante (Kao et al. 1995; Panagakos et al. 1996; Salcetti et al. 1997; Aboyoussef et al. 1998). O monitoramento dos níveis de IL-1β em sítios de implantes foi sugerido como mais efetivo no controle da periimplantite em relação a outros mediadores inflamatórios (Aboyoussef et al. 1998).

O antagonista do receptor da IL-1 (IL1-ra) compete com a IL-1 pela ocupação de receptores de superfície celular. Constitui-se um importante regulador endógeno do processo inflamatório (Tarlow et al. 1994). O IL-1ra parece regular a atividade da IL-1, funcionando como um inibidor competitivo do desenvolvimento de doenças mediadas pela IL-1 (Dinarello 1991) e tem sido utilizado como agente terapêutico em doenças de caráter imuno-inflamatório, como a artrite reumatóide (Heresbach et al. 1997; Buchs et al. 2001; Tolusso et al. 2006).

A análise dos níveis de interleucinas parece, dessa forma, ser um mecanismo de diagnóstico promissor para detectar a condição de perda de implantes dentais osseointegráveis em estágios precoces.

1.3 Polimorfismos em genes do *cluster* da IL-1

São conhecidos três genes reguladores da produção da IL-1. Os genes *IL1A* e *IL1B* produzem a IL-1α e a IL-1β, respectivamente. Já o terceiro gene, *IL1RN*, codifica a proteína denominada antagonista do receptor da IL-1 (IL-1ra). Esses genes (*IL1A*, *IL1B* e *IL1RN*) estão próximos e localizados no braço longo do cromossomo 2 (Nicklin et al. 1994). Os genes da *IL1A, IL1B* e *IL1RN* são potenciais candidatos como marcadores genéticos para condições inflamatórias, incluindo a periodontite e a periimplantite (Moreira et al. 2005; Laine et al. 2006).

Existem polimorfismos no conjunto de genes que regula a produção de IL-1 (Kornman & di Giovine 1998). Polimorfismos são alterações na seqüência gênica, que geram formas variantes, denominadas alelos, cuja freqüência do mais comum é menor que 99%. Na posição -889 do promotor do gene *IL1A* foi descrito um polimorfismo caracterizado pela substituição de uma base citosina (C) por uma timina (T), originando dois possíveis alelos: alelo C e alelo T (McDowell et al. 1995). Estudos demonstraram que pacientes que carregam o alelo T podem produzir níveis mais elevados da proteína IL-1α (Shirodaria et al. 2000). Na posição -511 do promotor e na posição +3954 do exon 5 do gene *IL1B* foram descritos polimorfismos bi-alélicos, caracterizados pela substituição de uma base C por T (Pociot et al. 1992). Os alelos T dos dois polimorfismos foram relacionados à produção aumentada da proteína IL-1β (Pociot et al.

1992). Foi observado que dois destes polimorfismos (alelo T do gene *IL1A*-889 e alelo T do gene *IL1B*+3954), quando juntos, estiveram associados à presença de periodontite severa em adultos não-fumantes (Kornman et al. 1997). Posteriormente, foi demonstrado desequilíbrio de ligação entre esses dois *loci* polimórficos (Asano & Magari 1976; Gore et al. 1998). Pacientes que portavam esse haplótipo, composto por alelos T de ambos os polimorfismos, foram denominados genótipo-positivos (Kornman et al. 1997). A presença de um dos polimorfismos (alelo T do *IL1B* +3954), que compõe o genótipo-positivo, está relacionada a uma produção duas a quatro vezes maior da IL-1β *in vitro* (Kornman et al. 1997; Kornman & di Giovine 1998). O alelo T do polimorfismo *IL1B* (C+3954T) parece estar implicado no risco e severidade a diversas doenças imuno-inflamatórias (Takamatsu et al. 2000; Karjalainen et al. 2002), inclusive a periodontite (Rogers et al. 2002; Moreira et al. 2005). No intron 2 do gene *IL1RN,* foi identificado um polimorfismo do tipo número variável de repetições em *tandem* (VNTR), caracterizado por uma seqüência de 86 pares de base (86 pb) que se repete em número variável. Este polimorfismo fornece cinco possíveis alelos, que correspondem à presença de 2, 3, 4, 5 ou 6 repetições dessa seqüência (Tarlow et al. 1994). O alelo 2 do gene *IL1RN* (intron 2) foi associado à produção diminuída da proteína IL-1ra (Andus et al. 1997; Tountas et al. 1999). Além disso, células mononucleares de portadores desse polimorfismo demonstraram produzir concentrações elevadas de IL-1β *in vitro* (Santtila et al. 1998). É provável que este polimorfismo aumente o nível de IL-1β, resultando em um desequilíbrio na relação IL-1β/IL-1ra o que conduz a um aumento da suscetibilidade ou uma resposta mais intensa para as doenças inflamatórias. O alelo 2 do *IL1RN* pode ser um indicador de doença inflamatória; porém, não necessariamente estar ligado a sua causa (Laine et al.

2006). Estudos têm mostrado uma associação entre o alelo 2 do *IL1RN* e diversas doenças inflamatórias e auto-imunes, como colite ulcerativa (Mansfield et al. 1994), lúpus eritematoso sistêmico (Blakemore et al. 1994), nefropatia diabética (Blakemore et al. 1996) e alopécia areata (Tarlow et al. 1994).

Recentemente, observou-se que, em indivíduos fumantes e portadores do genótipo-positivo, os implantes em função por pelo menos um ano apresentaram maior perda óssea marginal (Feloutzis et al. 2003; Gruica et al. 2004). A associação do fumo com o genótipo-positivo esteve também relacionada à suscetibilidade à perda de implantes dentais osseointegráveis (Jansson et al. 2005). Foi encontrada correlação significante entre o genótipo T/T do polimorfismo *IL1B* (C-511T) e a incidência de perda óssea periimplantar precoce (antes da instalação da prótese); enquanto a análise do genótipo-positivo não revelou associação significante (Shimpuku et al. 2003). Outros autores observaram ausência de associação entre o genótipo-positivo e a falha de implantes dentais osseintegráveis (Wilson & Nunn 1999; Rogers et al. 2002). Poucos estudos até o momento testaram a influência do polimorfismo no gene *IL1RN* na falha de implantes (Campos et al. 2005; Laine et al. 2006). Não foi observada associação entre polimorfismos em genes do *cluster* da *IL1* e a perda precoce de implantes em uma população brasileira (Campos et al. 2005). No entanto, os resultados obtidos são questionáveis, visto o limitado número de indivíduos analisados.

A propriedade de indução da reabsorção óssea demonstrada pela IL-1 e a presença de níveis elevados no fluido gengival de implantes com sinais de falha (Kao et al. 1995; Panagakos et al. 1996; Curtis et al. 1997; Aboyoussef et al. 1998; Rogers et al. 2002) sugerem que essas citocinas, bem como

polimorfismos em seus genes, podem ter influência na perda de implantes dentais osseointegráveis.

A resposta do hospedeiro parece ser determinante na destruição tecidual ao redor de implantes, afetando a osseointegração, intensificando a periimplantite e promovendo perdas ósseas marginais indesejáveis. Nesse contexto, mediadores pró-inflamatórios desempenham papel crucial. Polimorfismos nos genes que codificam citocinas inflamatórias podem alterar sua taxa de expressão, potencializando sua ação.

O aumento das citocinas inflamatórias pode indicar suscetibilidade às perdas e falhas nos implantes dentais. Marcadores genéticos permitem detectar indivíduos que produzem mais citocinas inflamatórias frente a estímulos mecânicos ou infecciosos. Esses marcadores podem permitir ao profissional a adequada seleção de pacientes, melhor planejamento do caso, estabelecimento de prognóstico seguro e instauração de terapêutica individualizada. Dessa forma, pode-se proporcionar o aumento do índice de sucesso dos implantes, tornando essa alternativa de tratamento cada vez mais previsível.

OBJETIVOS

2. OBJETIVOS

Identificar as principais causas de perda de implantes dentais osseointegráveis em pacientes do Instituto Latino Americano de Pesquisa e Ensino em Odontologia (ILAPEO), entre 1996 e 2006;

Investigar se alelos e/ou genótipos específicos dos polimorfismos gênicos *IL1RN* (intron 2) e *IL1B* (+3954) estão associados à perda de implantes dentais osseointegráveis nessa população.

ARTIGO 1

3. Artigo 1

(Submetido ao periódico *Implant Dentistry* em 15/08/2006)

Failing Factors Associated with Osseointegrated Dental Implant Loss

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ABSTRACT

Dental implants are currently the esthetic and functional alternative of choice for tooth absence. Despite the high success rate shown by longitudinal studies, failures do occur, even in patients who present appropriate clinical conditions. The aim of the present study was to identify factors related to or determinant of dental implant loss in patients of the Latin-American Dental Research Institute (ILAPEO), Curitiba, PR. Retrospective analysis of 3,578 records of patients who had placed implants in this institute during the period of 1996 to 2006 was performed. Beyond records, panoramic and periapical radiographies were analyzed. Out of 3,578 individuals implant treated, failures occurred in 126 (3.5%) patients (mean age 52.2 ± 10.6 years). Men lost more implants (4.5%) than women (3.1%) (p=0.05). Early failure represented the majority of failure cases (88.2%). The main detectable causes of implant loss were evaluated. Most implant losses (75%) did not present apparent clinical cause. Identified causes were: 17.5% iatrogenic conditions (surgical technique, contamination and/or occlusal trauma); poor bone quality and quantity (3%); peri-implantitis (1%), and 3.5% were misregistrations. Failure was more frequent when the implant was installed in the posterior jaw. The results obtained in this study suggest that host factors can be contributing for the implant failure.

KEY WORDS: dental implant failure, risk factors, osseointegration, host features.

Dental implants have become an important therapeutical modality in the last decades,[1,2] mainly after the works developed by Bränemark,[3] in which the direct contact between the bone functional tissues and the biomaterial titanium was termed osseointegration.[4]

After the installation of endosteous implants, there are three possible responses that may occur in host tissues: 1) acute or chronic inflammatory process, causing early implant failure; 2) the formation of connective tissue surrounding implant, leading to osseointegration failure, and 3) living and functional bone tissue formation around the implants, resulting in osseointegration.[5,6]

The success rate in patients who are treated with dental implants, in general, is high for all implant systems.[7,8] In prospective and retrospective studies, it varies from 84.9 to 100% in longitudinal studies up to 24 years.[9-12] However, despite the low number, failures occur, most of the times unexpectedly.[13-16] Beyond the implant loss, early marginal bone loss around endosteous implants is also considered a failure aspect.[17]

Implant loss is divided into early failure, before the occurrence of the osseointegration, and the late failure, after the implant receives occlusal load.[4,18-20] Success of osseointegration is defined as an association of functional and aesthetic results,[21,22] and depends on some factors,[23] like implant biomaterial and superficial properties (topography and roughness surface),[24-27] appropriate bone quantity and quality,[19] and non-occurrence of surgical complications, as bone overheating and contamination,[21,26,28-30] occlusal overload,[26] and peri-implantitis. [22,31]

Direct and indirect systemic factors, that influence host response, seem to be of great relevance in the identification of risk groups to implant loss. In some cases, even when the patient has appropriate bone quantity and quality, and adequate clinical indication and recommendations are followed, failures in the osseointegration process do still occur. According to Esposito et al. (1999a),[32] implant failure is related to immuno-inflammatory host response. An intense inflammatory process,[33] which compromises osseointegration,[34] can lead to implant loss. Failure in the osseointegration process is a significant cause of implant loss.[35]

The criteria for evaluation of implant failure are commonly based on clinical and radiographic alterations, which normally reflect wide pathological conditions.[33]

The identification of implant loss causative and related factors can allow early intervention and minimize injury, besides increasing therapeutical potential.[33,36]

The aim of this study was to identify, retrospectively, factors associated with the osseointegrated implant loss in patients from the Latin-American Dental Research Institute (ILAPEO), Curitiba/PR.

MATERIALS AND METHODS

In a retrospective study, 3,578 patient records from the Latin-American Dental Research Institute (ILAPEO) of Curitiba/PR were analyzed. These patients were implant treated (*NEODENT™ Implante Osteointegrável*) between 1996 and 2006. The known possible factors that led to implant failure were identified by means of record evaluation and analysis of complementary documentation (panoramic x-rays and periapical radiographies). Patient sex and age, number

of present teeth, number of placed implants, main detectable failure causes, duration of the implants, implant position, bone quality and quantity, and the primary stability were evaluated.

RESULTS

From the patients who were implant treated (n=3,578), most patients (2,459; 68.7%) were women and 1,119 (31.3%) were men (mean age 50±11.9 years). Most patients were non-smokers (88.5%). The majority of patients (95.5% men and 96.9% women) did not present implant loss.

Failures occurred in 126 (3.5%) patients (mean age 52.2±10.6 years). Out of these, 76 (60.3%) were women and 50 (39.7%) were men. Men lost more implants (50/1,119; 4.5%) than women (76/2,459; 3.1%) (p=0.05). Among the patients who lost implants, the average of present teeth in the moment of surgery was 19 (0 to 31). The baseline clinical parameters for patients with implant loss are shown in table 1.

From 875 placed implants in the failure group (6.9 per patient); 212 were lost (1.7 per patient). The percentage of implant loss in the implant failure group was 24.2%. Bone quality/quantity in most patients were considered to be adequate [bone type II/III and B/C (172/212; 81.1%)]. Most implants presented reasonable primary stability (≥ 45 N) (180/212; 84.8%). Clinical characteristics of implants placed in patients with implant failure are shown in table 2.

Early failure represented 88.2% (187/212) of cases; only 7.5% (16/212) occurred after loading, and 4.2% (9/212) were missed after immediate load. The survival implant mean time in early failure implants was 30.5 weeks (0 to 179.0), and in late failure implants was 72.5 weeks (4.0 to 191.3), and the survival mean time in immediate load was 4.4 weeks (1.9 to 6.0).

The identified causes of implant failure were iatrogenic conditions, as inadequate surgical technique and contamination, and occlusal trauma (17.5%; 37/212), poor bone quality and quantity (3%; 6/212), and peri-implantitis (1%; 2/212). Misregistrations were found in 3.5% (7/212) of cases. The majority of patients (75%; 160/212) did not present any failure apparent clinical cause.

Failure was more frequent when the implant was installed in the posterior jaw (sextants IV and VI) (124/212; 58.5%).

DISCUSSION

Epidemiologic and retrospective studies are important for the knowledge of the prevalence of clinical aspects influencing implant failure, constituting a reference point for specialists to plan, execute and evaluate implant procedures. The challenge for the future in the treatment with osseointegrated implants will be the professional ability to detect and classify risk. The professional team must be able to select therapeutic procedures taking into consideration individual features,[37] trying to minimize injury and failure.

The technique of installation of osseointegrated implants presents predictable and replicable results, with levels of success over 90%.[38] Randomized clinical trials comparing different implant types/systems with a follow up of at least one year reporting results of 512 patients showed no significant differences concerning implant failures and minor statistically significant differences for peri-implant bone level changes.[39]

In the present study, the number of patients who presented implant loss was 126 (3.5%), which is in accordance with published data from longitudinal studies.[19,40] It was observed that implant loss was influenced by sex. Men were more prone to develop implant failure (p=0.05), which is in accordance with the

study by Mau.[41] No statistically significant difference among patients was observed for age. A lack of association between implant failure and age were also observed by other authors.[19,37,42-47]

It was observed in this study that the group of patients with implant loss was partially edentulous at the surgery moment. The success rate has considered to be lower in partially than in totally edentulous patients.[40] This difference can partially be explained by a more favorable load distribution[32] and lack of remaining teeth bacterial reservois.[14,48]

Early failure results from a disturbance in the initial steps of the osseointegration mechanisms.[4,40,42] The majority of failures occurred in the pre-load phase (88.2%). After the occurrence of osseointegration, 7.5% of the implant failures occurred after loading, and only 4.2% occurred in immediately loaded implants. This observation points to a host response role on the individual healing process.[33-35,43]

Iatrogeny was the identified cause of implant failure in 17.5% of cases. Other studies have evidenced a similar failure prevalence caused by iatrogenic factors,[43-45,49] like contamination,[46,50-52] overheating,[47,53] occlusal trauma,[54] inadequate surgical technique,[53] overloading forces.[43,47]

Poor bone quality and quantity have also been considered a determinant influence in the implant failure.[19,43,50,55,56] Studies suggest that most failures occur in places of poor bone quantity and quality.[50,54-58] However, in this study, bone quality and quantity were considered adequate in the great majority of patients (81.1%) [bone type II/III and B/C]. Only 3% of the implant failures were related to poor bone quantity and quality. The found primary stability, in this study, was considered to be reasonable (84.8%) for most patients. This indicates that the surgical technique was performed in an adequate way.[59] This

still corroborates with other studies, which affirm that combined B and C bone quantity, together with II and III quality, allows a satisfactory stabilization and an adequate osseointegration.[9,60-66]

A small percentage of patients (1%) presented peri-implantitis as the identified main cause of implant loss. A large number of studies have reported peri-implantitis as an important cause of implant failure.[19,22,31,50,51]

In the present study, 58.5% of the patients who presented failure had lost implants installed in the posterior region of the jaw (sextants IV and VI). This is maybe due to local bone quality and quantity. The jaw cortical layer generally is dense and thick and tends to become narrower and porous in the posterior region. The same occurs with the trabecular portion. Moreover, the presence of the mandibulary canal limits the available bone volume in the posterior jaw region.[32,67]

Despite several studies reporting various clinical causes in association with osseointegrated implant failures, some questions on risk factors, which predispose to implant loss, remain to be clarified.[7,15, 54]

The great majority of patients (75%) with lost implants do not present apparent determinant clinical causes,[9,10,68] suggesting an inefficient host immuno-inflammatory response.[54] Besides, failures concentrated in a small group (126/3,578 patients; only 3.5%). In this group, the percentage of lost implants was 24.2%.These data point to the clusterization phenomenon, which claims that few individuals concentrate risk to implant loss.[4,69-71]

From this observation, several questions should arise in the search for implant loss susceptibility. Genetic predisposition could be suggested, including the adding effect of gene polymorphisms.

CONCLUSION

Most patients presented no apparent clinical cause for implant failure. These results suggest that host factors, not identified clinically, may contribute to increase risk for implant loss.

Genetic studies might be proposed in order to better understand host response to implant failure.

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Table 1. Baseline clinical parameters of patients who presented implant failure (n=126 patients).

		n (%)
Gender	male	50 (39.7)
	female	76 (60.3)
Age		
mean (± SD)	male	50.1 (10.8)
	female	53.2 (10.5)
Smoking	yes	19 (15.1)
	no	107 (84.9)

Table 2. Clinical characteristics of placed implants in patients who presented implant failure (n=212 lost implant, n=663 successful implants)

		n (%)
Failed and successful implants	success	663 (75.8)
	failure	212 (24.2)
Primary stability	> 40 N	180 (84.8)
	≤ 40 N	32 (15.2)
Bone quantity/quality	*adequate	172 (81.1)
	non-adequate	40 (18.9)
Bone graft	yes	29 (13.7)
	no	183 (86.3)
Implant design	cylindrical	184 (86.8)
	conical	28 (13.2)
Implant hexagon	internal	164 (77.3)
	external	48 (22.7)
Implant loss	early	187 (88.2)
	late	16 (7.5)
	immediate loading	9 (4.3)

*quantity II or III / quality B or C

ARTIGO 2

4. Artigo 2

ANALYSIS OF THE ASSOCIATION OF *IL1B* (C+3954T) AND *IL1RN* (INTRON 2) POLYMORPHISMS WITH OSSEOINTEGRATED IMPLANT LOSS IN A BRAZILIAN POPULATION

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ABSTRACT

Dental implants have become an important therapeutical modality for tooth replacement. Although the high success rate showed in longitudinal studies, failures occur, even in patients who present appropriate clinical conditions. Together with the clusterization phenomenon, which is the presence of multiple implant losses in the same group of individuals, this fact suggests that host response aspects may influence the implant failure process. However, little is known about the influence of genetic susceptibility on implant loss. IL-1*β* and IL-1ra are believed to play a key role in immunological reactions and inflammation. Polymorphisms *IL1B* (C+3954T) *and IL1RN* (intron 2 – 86 bp variable number of tandem repeats) are evidenced to alter the expression of the coding proteins. Higher levels of IL-1*β* were found in diseased implant sites, which could be a molecular indicator of implant failure. The aim of this study was investigate the association between failure of dental implants and the functional polymorphisms *IL1B* (+3954) *and IL1RN* (intron 2). The study population (n=266) was obtained from the patient pool treated in the Latin American Dental Research Institute (ILAPEO), and divided into: *Test group (T)* - 90 subjects with implant loss, and *Control group (C)* - 176 subjects with at least one implant in function for at least six months. The patients were matched by sex, age and smoking status. Patients' socioeconomic profile, general medical condition, hygiene parameters, and clinical measurements such as number of teeth and periodontal status were analyzed. Genomic DNA from oral mucosa was amplified by polymerase chain reaction (PCR). The fragments were submitted to agarose gel electrophoresis, followed by ethidium-bromide staining method. Polymorphisms *IL1B* (+3954) and *IL1RN* (intron 2) were in Hardy-Weinberg equilibrium. Regarding clinical aspects, the following parameters were observed to influence implant failure: edentulism, probing pocket depth, and number of present teeth. No differences in genotype distribution and allele frequencies between C and T groups were found for *IL1B* (+3954) and *IL1RN* (intron 2) polymorphisms in the study population. It was observed that clinical parameters, but not the study polymorphisms, were associated to implant loss.

INTRODUCTION

Dental implants have become an important therapeutical modality in the last decades, mainly after the studies developed by Bränemark (Branemark et al. 1969; Albrektsson et al. 1981; Smith 1985), in which the direct contact between the bone and titanium surface was termed osseointegration (Att & Stappert 2003; Henry 2005).

Dental implant success is defined as an association of functional and aesthetic results (Albrektsson et al. 1986), and depends on some factors like implant biomaterial (Smith & Zarb 1989; Porter & von Fraunhofer 2005), superficial properties such as topography and roughness (Haraldson 1980; Albrektsson et al. 1981; Albrektsson 1983; Carlsson et al. 1986), and appropriate bone quantity and quality (Esposito et al. 1999). Besides, successful implant procedures result from a non-occurrence of surgical complications, as bone overheating and contamination (Albrektsson et al. 1981; Lavelle et al. 1981; Eriksson & Albrektsson 1983; Eriksson & Albrektsson 1984; Albrektsson & Hansson 1986), occlusal overload (Albrektsson et al. 1981), and peri-implantitis (Smith & Zarb 1989; Panagakos et al. 1996; Esposito et al. 2005b).

The success rate in patients who are treated with dental implants is high for all implant systems (Scolozzi & Jaques 2004; Esposito et al. 2005a). In prospective and retrospective studies, it varies from 85 to 100% (Adell et al. 1990; Bain & Moy 1993; Bain 1996; Lekholm et al. 1999). However, despite the low prevalence, failures occur, most of the times unexpectedly. Regarding the moment of occurrence, failures can be classified as early, when osseointegration fails to occur, or late, when the achieved osseointegration is lost after a period in function (Esposito et al. 1998a).

Studies have demonstrated that the covering material of the implants, considered inert, can stimulate immunogenic cells to produce inflammatory mediators, such as interleukins (IL) (Perala et al. 1992; Harada et al. 1996). These cytokines have been considered to have a key role in the regulation of the inflammatory and immunological host response (Esposito et al. 1998b). An intense inflammatory process could impair osseointegration (Kao et al. 1995; Scaglioni & Deliga 1996), and lead to implant loss. In fact, failure in the osseointegration process is the main cause of implant loss (Bianchi et al. 2003).

In order to clarify the implant failure mechanisms, several studies have investigated tissues surrounding unsuccessful dental implants (Eley et al. 1991; Kao et al. 1995; Panagakos et al. 1996; Curtis et al. 1997; Salcetti et al. 1997; Teronen et al. 1997; Aboyoussef et al. 1998; Ruhling et al. 1999). An abnormal immune-inflammatory response involving different cell types such as macrophages, polymorphonuclear neutrophils, T and B lymphocytes, endothelial cells, fibroblasts, keratinocytes, osteoclasts and osteoblasts can destroy the peri-implant and periodontal tissues (Adell et al. 1986; Lekholm et al. 1986; Seymour et al. 1989). If activated, these cells can synthesize and release cytokines (Dewhirst et al. 1985; Lindemann et al. 1988; Bom-van Noorloos et al. 1990; Saglie et al. 1990; Dongari-Bagtzoglou & Ebersole 1998; Gainet et al. 1998; Salvi et al. 1998), which mediate both the inflammatory and the osteolytic processes. In an attempt to establish diagnostic markers for monitoring implant health status, levels of interleukins have been measured in diseased implant sites (Kao et al. 1995; Panagakos et al. 1996; Curtis et al. 1997; Salcetti et al. 1997). Higher levels of IL-1β were found in diseased implant sites when compared to healthy ones (Kao et al. 1995; Panagakos et al. 1996;

Curtis et al. 1997; Aboyoussef et al. 1998), suggesting that such inflammatory mediators are associated with implant failure (Salcetti et al. 1997).

The IL-1 gene cluster has been mapped to the long arm of chromosome 2 and consists of three genes: *IL1A, IL1B* and *IL1RN,* encoding IL-1*α*, IL-1*β* and IL-1ra, respectively (Nicklin et al. 1994). The IL-1*α* and IL-1*β* have several pro-inflammatory activities (Dinarello 1991), causing strong stimulatory effects on bone resorption and inhibitory effects on bone formation (Stashenko et al. 1987; Nguyen & Samama 1991; Tatakis 1993). The IL-1ra is a natural antagonist of both IL-1*α* and IL-1*β*, acting by binding the IL-1 receptors inhibiting biological response (Lennard 1995).

The knowledge that implant failure tends to cluster in subsets of individuals (Weyant & Burt 1993; Hutton et al. 1995) may indicate that specific host characteristics that disturb the osseointegration process are influenced by genetic factors (Santos et al. 2002).

Gene polymorphisms are a mechanism by which individuals may exhibit variations and were shown to be associated with disease susceptibility (Trevilatto et al. 2003). Most polymorphisms are single nucleotide exchanges (SNPs) that occur in a high frequency in the human genome (Venter et al. 2001) and may affect the function of genes (Hu et al. 2005).

Specific interleukin IL-1 gene polymorphisms have been associated with an increased susceptibility to inflammatory diseases, including periodontitis (Tai et al. 2002; Li et al. 2004; Moreira et al. 2005; Scapoli et al. 2005), and augmented likelihood of tooth loss during the maintenance phase after conventional periodontal therapy (De Sanctis & Zucchelli 2000). Some studies suggested one significant association between the IL-1 alleles/genotypes with

implant failure (Feloutzis et al. 2003; Shimpuku et al. 2003; Gruica et al. 2004; Jansson et al. 2005), and peri-implantitis (Laine et al. 2006).

There is a single study investigating the association between *IL1* gene polymorphisms and implant failure in the Brazilian population. However, besides the low number of individuals, only early implant failure was considered. Thus, the aim of the present study was to evaluate the impact of *IL1B* (+3954) and *IL1RN* (intron 2) polymorphisms on dental implant loss in a Brazilian population.

METHODS

Subject selection

In this study, 3,578 patient records from the Latin-American Dental Research Institute (ILAPEO) of Curitiba/PR were analyzed. These patients were implant treated (*NEODENT™ Implante Osteointegrável*) between 1996 and 2006. Out of 3,578 individuals implant treated, 126 patients (3.5%) presented implant loss. From these 126 patients, 90 individuals composed the test group (T). The control group (C) was composed of 176 patients treated with osseointegrated implants, with at least one implant in function for more than six months and without any failure. The convenient sample presented 266 unrelated, both gender, mean age 51.5 ± 11.5 (range 25 to 85) years. The patients selected for study from the ILAPEO Dental Clinics were matched by gender, age, and smoking (Table 1). The study sample was from the Southern region of Brazil. Although the study sample were mostly composed by Caucasian, the Brazilian white population is heterogeneous. Recent articles have not recommended grouping Brazilians into ethnic groups based on color, race and geographical origin because Brazilian individuals classified as white or black have significantly overlapping genotypes, probably due to miscegenation (Parra et al.

2003). According to the Brazilian Government Census 2005, in the Brazilian Southern region, the prevalence of white is 77.8%, black, 2.2%, mulatto, 18.9%, and japanese, 1.1%. Reporting the white population, there is a predominance of Italian, Spanish, and Portuguese heritage. The study population was composed mainly of Caucasians.

Patients signed a consent form within a protocol approved by an Institutional Review Board, after being advised of the nature of the study (approved by the Ethical Committee in Research at PUCPR, protocol 323). Subjects answered a personal, medical and dental history anamnesis, as well as had their socioeconomic profile assessed according to Brazilian Economical Classification Criteria (ABEP 2003). Subjects in good general health could not have any of the following exclusion criteria: HIV infection, current pregnancy or lactation, orthodontic appliances, present necrotizing ulcerative gingivitis and periodontitis, and history of aggressive periodontitis.

Table 2 shows patients' socioeconomic profile, general medical condition, current medication, tooth brushing, use of dental floss and mouthwash, dental appointment frequency, and clinical measurements such as number of teeth and placed implants.

Periodontal Status

Measurements of probing pocket depth (PPD) and clinical attachment loss (CAL) were recorded at four points around each tooth. The following parameters were recorded: gingival index (GI) (Loe & Silness 1963); plaque index (PI) (Silness & Loe 1964), calculus index (CI) (Greene & Vermillion 1964), and mobility (absent or present). The periodontal status of all subjects is shown in table 3. Periodontal index were recorded from each site using a conventional

U.N.C periodontal probe, Hu-Friedy™ (Chicago, IL, USA). All clinical data were collected by one examiner (F.A.P.).

DNA collection and purification

From all subjects, epithelial buccal cells were sampled according to described procedure (Trevilatto & Line 2000). DNA was extracted from epithelial buccal cells with ammonium acetate 10 M and EDTA 1 mM (Aidar & Line 2007).

Analysis of genetic polymorphisms

Polymorphism in the IL1B gene at position +3954 (exon 5)

The following primer pair was used for polymerase chain reaction (PCR) amplification of genomic DNA samples: 5'- CTC AGG TGT CCT CGA AGA AAT CAA A - 3' and 5' - GCT TTT TTG TGT GAG TCC CG - 3'. One microliter of the genomic DNA was used for PCR amplification in a reaction mixture containing 22.5 µL PCR Supermix (Invitrogen Life Technologies, Carlsbad, CA, USA), and 0.5 µL of each primer (25 µM). The reactions were performed in a *Techne* 7-572 thermal cycler. Cycling parameters were as follows: an initial denaturation step for 5 min at 95ºC, followed by 40 cycles of denaturation for 1 min at 95ºC, primer annealing at 56ºC for 1 min, extension at 72ºC for 1 min, and a final extension step of 72ºC for 7 min. The restriction fragment length polymorphism (RFLP) technique was performed in a final reaction volume of 20 µL, using 2 U T*aq*I and 10 µL aliquot of PCR products digested at 65°C overnight (ON) to yield allele C (85 + 97 + 12 bp) and allele T (182 +12 bp). The restriction fragments were analyzed in 1.8% agarose gel electrophoresis. The gels were stained with ethidium bromide and photographed under ultraviolet light. The genotypes were determined by comparing the RFLP band patterns with a 1 kb plus DNA ladder (Invitrogen Life Technologies).

Polymorphism in intron 2 of IL1RN gene

The following primer pair was used: 5'-CTC AGC AAC ACT CCT AT-3' and 5'-TCC TGG TCT GCA GGT AA-3'. One microliter of the genomic DNA was used for PCR amplification in a reaction mixture containing 22.5 µL PCR Supermix (Invitrogen Life Technologies, Carlsbad, CA, USA), and 0.5 µL of each primer (25 µM). The reactions consisted of an initial denaturation step of 5 min at 95ºC, followed by 40 cycles of 1 min at 95ºC, 1 min at 48ºC, extension at 72ºC for 1 min, and a final extension step of 72ºC for 7 min. In the second intron of *IL1RN* gene, five alleles were defined by different numbers of a 86 bp segment repeat. Genotypes were determined by comparing the size of the bands with a molecular weight ladder, with separation into allele 1 (4 repeats - 412 bp), allele 2 (2 repeats - 240 bp), allele 3 (3 repeats - 326 bp), allele 4 (5 repeats - 498 bp), and allele 5 (6 repeats - 584 bp). Amplification products were analyzed in 1.4% agarose gel electrophoresis. The gels were stained with ethidium bromide and photographed under ultraviolet light.

Statistical analysis

Nominal variables were expressed as frequencies and percents. To assess association between nominal variables, Chi-square (χ^2) test or Fisher's exact test was performed. Continuous variables were expressed as mean and standard deviation and Student's t-test was used to compare means between two groups. U-Mann Whitney was used when continuous variables presented non-normal distribution. For continuous variables, Kruskal-Wallis test was used to assess differences among groups, because non-normal distributions were observed. Multivariate analysis was performed by Logistic Regression model. A *p*-value < 0.05 was considered statistically significant. Statistical analysis was

performed using statistical software SPSS 10.0 for Windows (SPSS Inc, Chicago, IL).

RESULTS

No statistically significant differences (*NS*) were observed in the social profile. Most individuals from the two groups belong to A1, A2 and B1 socioeconomic class, indicating a social status above the population average, according to Brazilian Government Census 2005. General medical condition, current use of medication, tooth brushing, use of dental floss, mouth washing, and clinical appointment frequency showed *NS* between groups without (C) and with (T) implant loss.

There were significantly more edentulous patients in C (34/176; 19.3%) than in T (7/90; 7.8%) (p=0.019). However, the average present teeth in partially edentulous was higher in C (20.4 ± 6.3) than in T (18.4 ± 7.0) (p=0.038). The mean number of placed implants was increased in T (5.8 ± 3.5) than in C (4.5 ± 3.2) (p=0.002) (Table 2).

Evaluating the periodontal status, statistical significant differences (*SSD*) were found only in probing pocket depth (PPD) parameter between C (2.7 ± 0.5) and T (2.5 ± 0.5) (p=0.001) (Table 3).

Most failures were observed to occur before loading 119/148 (80.4%).

Polymorphisms *IL1B* (+3954) and *IL1RN* (intron 2) were consistent with the assumption of Hardy-Weinberg equilibrium. There was *NS* in the genotype distribution between patients with successful and failed implants for polymorphisms *IL1B* (+3954) (p=0.526) and *IL1RN* (p=0.803); nor was observed any *SSD* between the groups in the allele frequency for polymorphisms *IL1B* (+3954) (p=0.925) and *IL1RN* (p=0.608). Table 4 shows

the allele and genotype distributions for *IL1B (+3954)* and *IL1RN* (intron 2) gene polymorphisms in the control and test groups. The genotype frequencies and the allele distribution for the study polymorphisms are shown in figure 1 and 2, together with genotype and allele distributions of the study polymorphisms among different populations for comparison. In addition, no association was observed between genotypes/alleles of the study polymorphisms and any of the patients' periodontal parameters or systemic conditions.

The lack of association of the polymorphisms with implant failure was still observed after Logistic Regression model has been performed, considering sex, age, smoking, number of teeth, presence of diabetes, rheumatoid diseases, hypertension, and use of medication.

DISCUSSION

Dental implant success is directly related to the establishment of osseointegration. Bone is a dynamic tissue continuously remodeled through resorption and formation, mediated by local production of inflammatory cytokines, such as interleukins (Tatakis 1993; Parfitt 1994). These cytokines are believed to play a key role in immunologic reactions and inflammation (Esposito et al. 1998b). An exacerbated inflammatory process could impair osseointegration (Scaglioni & Deliga 1996, Kao et al. 1995).

Interleukin-1β has several pro-inflammatory activities on bone resorption (Stashenko et al. 1987; Nguyen & Samama 1991; Tatakis 1993). Interleukin-1 receptor antagonist inhibits IL-1β activity by competitive binding to the IL-1β receptor, thus suppressing the IL-1β induction of cytokine (Niimi et al. 2000). It may therefore play a crucial role acting as an important endogenous regulator of inflammation (Dinarello 1991; Lennard 1995).

The functional genetic polymorphisms *IL1B* (+3954) and *IL1RN* (intron 2) may account for variation in the production of IL-1β and IL-1ra proteins (Pociot et al. 1992; Tarlow et al. 1994; Hu et al. 2005). Since IL-1β and IL-1ra may function as immunomodulators of inflammation (Roberts et al. 1997), allelic variation in those genes could be expected to have an impact on inflammatory processes which might result in implant failure (Laine et al. 2006; Lachmann et al. 2007).

Association between polymorphisms in genes of IL-1 cluster and implant failure was investigated in several populations with different results (Table 5). A *NS* evidence of an increased risk to implant failure for patients presenting certain alleles of IL-1α and β polymorphisms was reported (Wilson & Nunn 1999; Rogers et al. 2002; Campos et al. 2005). However, alleles of IL-1α and β gene polymorphisms were correlated to marginal bone loss before the second stage surgery (implant load) (Shimpuku et al. 2003). When smoking and non-smoking groups were compared, it was found an increased risk for peri-implant bone loss, during the after loading phase, in a heavy smoking population positive for IL-1α and β polymorphisms (Feloutzis et al. 2003; Gruica et al. 2004). In agreement, in a partially edentulous group treated for periodontal disease prior to implant treatment, a synergistic effect of IL-1 positive-genotype and smoking was detected; characterizing individuals with these two conditions together as a population at higher risk for implant failure (Jansson et al. 2005).

With respect to Brazilian populations, there have not been observed differences in the allele and genotype frequencies between control and implant failure groups (Campos et al. 2005). However, this reported study was carried out with a low number of individuals, and only considering implant early failure. In this study, it was not observed an association of *IL1B* (+3954) and *IL1RN*

(intron 2) polymorphisms with implant failure, in agreement with other studies (Wilson & Nunn 1999; Rogers et al. 2002; Campos et al. 2005).

The genotype frequencies and the allele distribution for the study polymorphisms were similar to those reported for Caucasian Europeans in an Italian population (Tolusso et al. 2006) and for Caucasian Brazilians (Campos et al. 2005). The observed data may reflect the strong European heritage for the population from the Southern Brazil, as reported by the Brazilian Government Census 2005.

It was observed a major percentage of edentulism in C (34/176; 19.3%) when compared to T (7/90; 7.78%) (p=0.019). The *bacterial reservoir* in the remaining teeth can be considered a risk factor for implant failure (Apse et al. 1989; Ellen 1998). In fact, partially rather than totally edentulous showed more failure implants (Esposito et al. 1998a). However, partially edentulous subjects in C (20.4 ± 6.3) presented a higher mean number of present teeth than in T (18.4 ± 7.0) (p=0.038). Implants could be better maintained in function when a more favorable distribution of masticatory forces, together with adequate anatomical conditions, are present (Esposito et al. 1998b).

The periodontal status did not show *SSD* in the plaque index (PI), gingival index (GI), calculus index (CI), clinical attachment loss (CAL), and tooth mobility between the groups. Higher probing pocket depth (PPD) was found in C, but the difference of 0.18 mm between the groups may not be considered clinically relevant.

Most failures occurred before loading (80.4%) characterizing a predominance of early implant failure. This observation points to a host response role on the individual healing process (Kao et al. 1995; Scaglioni & Deliga 1996; Bianchi et al. 2003; Piattelli et al. 2003).

Implant loss can be attributed to several factors such as biological, microbiological and biomechanical (Esposito et al. 1998b; el Askary et al. 1999; Machtei et al. 2006). However, in some situations, clinical factors alone do not explain why some patients develop implant loss, which makes the cause and mechanism of the implant failure still obscure. This observation together with the phenomenon of clusterization, which indicates that multiple implant loss occurs in the same group of patients, support the evidence that individual characteristics mediated by genetic host response may play a role in the failure process (Tonetti 1999; Esposito et al. 2005b).

Considering that i) IL-1 mediators play an important role in inflammatory conditions, and ii) the study polymorphisms are reported to have the ability to produce higher levels of IL-1, the lack of association between IL-1 gene cluster functional polymorphisms and susceptibility to implant failure, showed by most studies in different populations, may point to a small contribution of these common genomic variations in the determination of complex traits such as implant loss.

Polymorphisms in several genes of the immune-inflammatory response can account together to genetic susceptibility to implant failure. In this context, the novel approach termed association based *case-control genomic scan*, which can genotype more than 100,000 SNPs at a time could be a good choice. Despite the high cost and the needs for sophisticated statistical tools, this could provide contribution for effective screening and treatment, and increase the understanding of why some patients do not respond to currently available treatments while others do.

CONCLUSION

The results obtained in this study suggest that: i) genetic polymorphisms *IL1B* (+3954) and *IL1RN* (intron 2) were not associated with implant failure in the study population; ii) clinical factors such as edentulism, and number of present teeth were related to osseointegrated dental implant failure.

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Table 1. Baseline characteristics of all sampled subjects (n=266).

	Control group (n=176)		Test group (n=90)		
	n	%	n	%	*p* value
Ethnic group					
Caucasian	167	95	89	99	* 0.172
Non-caucasian	9	5	1	1	
Age (years)‡	51.14 ± 11.49		53.20 ±10.82		† 0.160
Gender					
Female	117	66	56	62	* 0.499
Male	59	34	34	38	
Smoking					
Yes	40	23	18	20	*0.641
No	136	77	72	80	

*Fisher's test;
‡ Number-Mean ± Standart Deviation;
†Student's t-test.

Table 2. Patients' clinical findings (n=266).

	Control group (n=176)		Test group (n=90)		
	n	%	n	%	*p* value
Social profile					
A1/A2/B1	93	53	46	51	*0.797
B2/C/D	83	47	44	49	
General medical condition					
Systemic disease	53	32	23	26	*0.323
Diabetes	9	5	1	1	*0.172
Rheumatoid diseases	31	18	25	28	*0.058
Osteoporosis	3	2	2	2	*0.996
HAS[a]	31	18	24	27	*0.109
Cardiovascular diseases	10	6	8	6	*0.316
Hypotireoidism	18	10	10	11	*0.834
Medical treatment					
Yes	106	60	47	52	*0.239
No	70	40	43	48	
Current medication					
Any medication	103	59	48	53	*0.435
Antihypertension	28	16	21	23	*0.180
Antimicrobials	13	7	8	9	*0.640
AINES[b]	6	3	6	7	*0.229
AIES[c]	4	2	3	3	*0.691
Hormony reposition	40	23	23	24	*0.761
Estatinas	7	4	4	4	*0.999
Brushing daily					
1 to 3 times	128	73	70	78	*0.458
More than 3 times	48	27	20	22	
Dental floss daily					
Yes	141	77	68	72	*0.431
No	35	19	22	23	
Mouth washing daily					
Yes	96	52	45	48	*0.517
No	80	43	45	48	
Clinical appointments[‡]	6.0 ± 4.4		6.2 ± 4.8		[†]0.868
Clinical measurements					
Edentulism	34	19	7	6	*0.019
[#]Present teeth[‡]	20.4 ± 6.3		18.4 ± 7.0		[†]0.038
[#]Placed implants[‡]	4.5 ± 3.2		5.8 ± 3.5		[†]0.002

* Fisher's test;
[†] U-Mann-Whitney's test;
[‡] Number-Mean ± Standart Deviation;
[a]High blood pressure;
[b]Anti-inflammatory nonsteroidal drugs;
[c]Anti-inflammatory steroidal drugs;
[#]Control group (n=142); Test group (n=83).

Table 3. Periodontal status of partially edentulous patients (n=225).

Periodontal Status	**Control Group (n=142)**	**Test Group (n=83)**	
			p value
Gingival Index †	0.63 ± 0.38	0.65 ± 0.53	* 0.561
Plaque Index †	0.12 ± 0.24	0.24 ± 0.42	* 0.834
Calculus Index †	0.07 ± 0.12	0.13 ± 0.24	* 0.134
PPD [a] (mm) †	2.72 ± 0.46	2.54 ± 0.47	** 0.011
CAL [b] (mm) †	3.61 ± 0.85	3.67 ± 1.07	** 0.786
Mobility (absence/presence)	124 / 18	67 /16	‡ 0.247

* U-Mann-Whitney's test;
**Student's t-test;
‡ Fisher's test;
† Mean ± Standart Deviation;
[a] Probing pocket depth;
[b] Clinical attachment level.

Table 4. Genotype and allele frequencies of *IL1B* (+3954) and *IL1RN* (intron 2) polymorphisms of all sampled subjects.

	Control group (n=176)		**Test group (n=90)**		
***IL1B* (+3954)**	n	%	n	%	*p* value
Genotypes					
C/C	106	60	52	58	
C/T	62	35	36	40	*0.526
T/T	8	5	2	2	
[#]**Alleles**					
C	274	78	140	78	*0.925
T	78	22	40	22	
***IL1RN* (intron 2)**	n	%	n	%	*p* value
Genotypes					
1/1	100	57	47	52	
1/2	49	28	29	32	*0.803
2/2	21	12	12	13	
Others	6	3	2	3	
[#]**Alleles**					
1	255	72	125	69	
2	91	26	53	29	*0.608
Others	6	2	2	2	

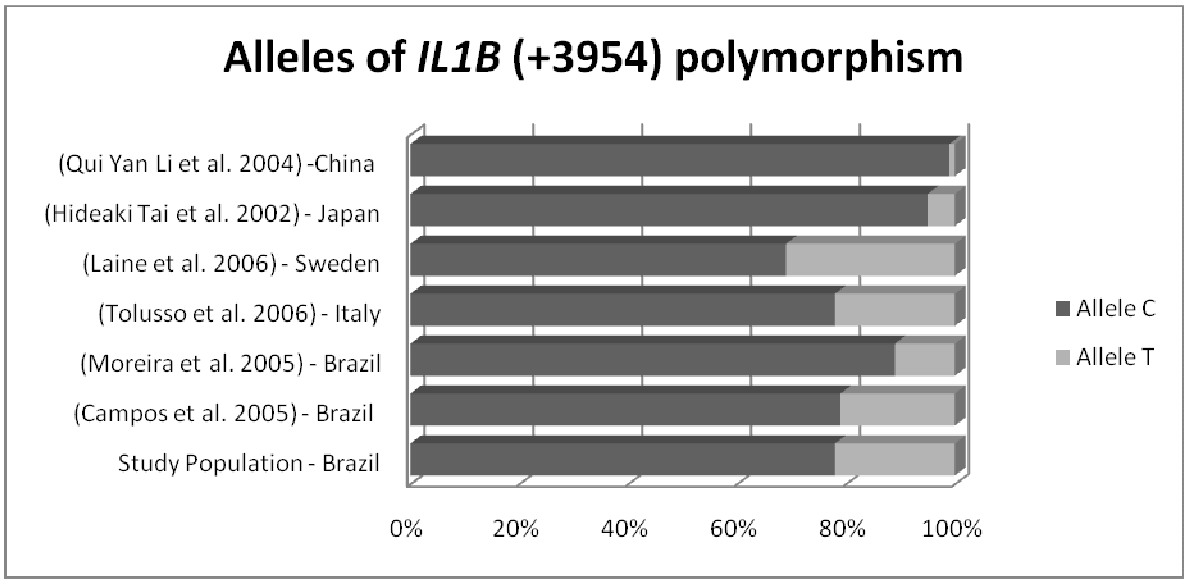
*Chi-square's test;

[#]Control group (n=352), Test group (n=180).

Table 5. Functional impact of the *IL1* gene polymorphisms investigated for susceptibility to implant failure

Authors	Polymorphisms	Case (n) / Control (n)	Population	Results
Wilson & Nunn 1999	*IL1A* (-889) and *IL1B* (+3954)	27/38	?	Not associated with implant failure
Rogers et al. 2002	*IL1A* (-889) and *IL1B* (+3954)	19/31	Australian Caucasian	Not associated with implant failure
Feloutzis et al. 2003	*IL1A* (-889) and *IL1B* (+3954)	51/39	European Caucasian	Smoking + IL1 positive genotype associated with marginal bone loss
Shimpuku et al. 2003	*IL1A* (-889) and *IL1B* (-511,+3954)	17/22	Japanese	Associated with marginal bone loss
Gruica et al. 2004	*IL1A* (-889) and *IL1B* (+3954)	34/146	European Caucasian	Smoking + IL1 positive genotype associated with marginal bone loss
Campos et al. 2005	*IL1A* (-889), *IL1B* (-511,+3954), and *IL1RN*	28/34	Brazilian	Not associated with implant early failure
Jansson et al. 2005	*IL1A* (-889) and *IL1B* (+3954)	6/16	European Caucasian	Smoking + IL1 positive genotype associated with marginal bone loss
Laine et al. 2006	*IL1A* (-889), *IL1B* (-511,+3954), and *IL1RN*	71/49	North Swedish Caucasian	That *IL1RN* gene polymorphism associated with peri-implantitis

Figure 1. Genotype/allele frequencies of *IL1B* (+3954) polymorphism in different populations.



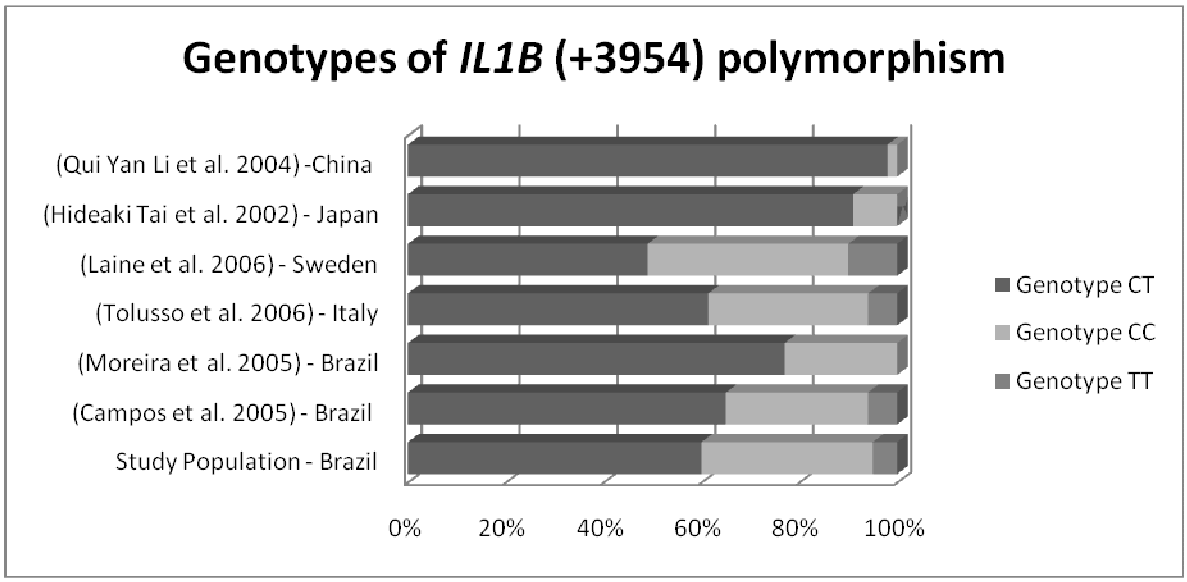
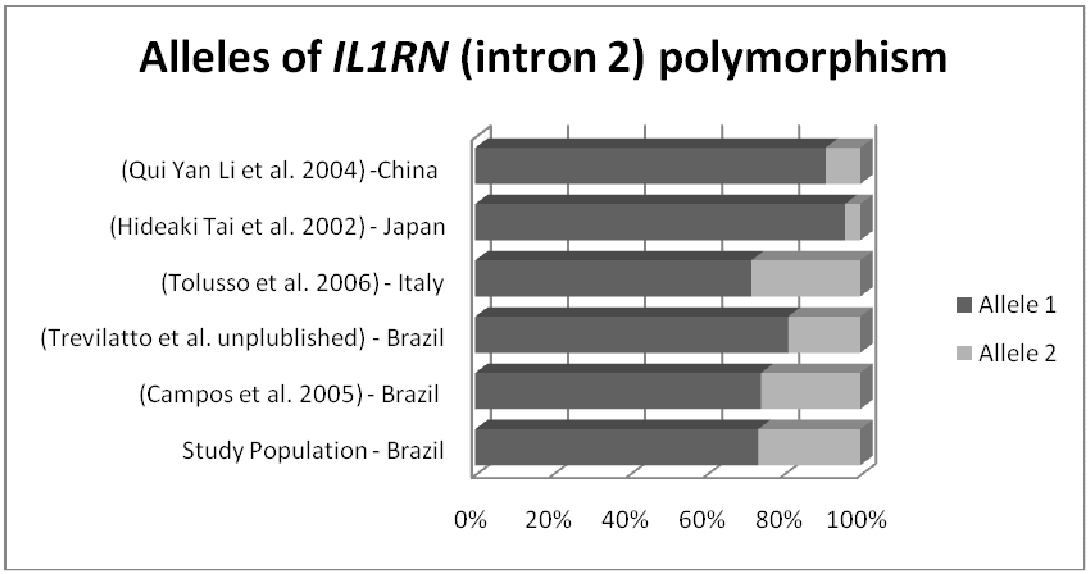
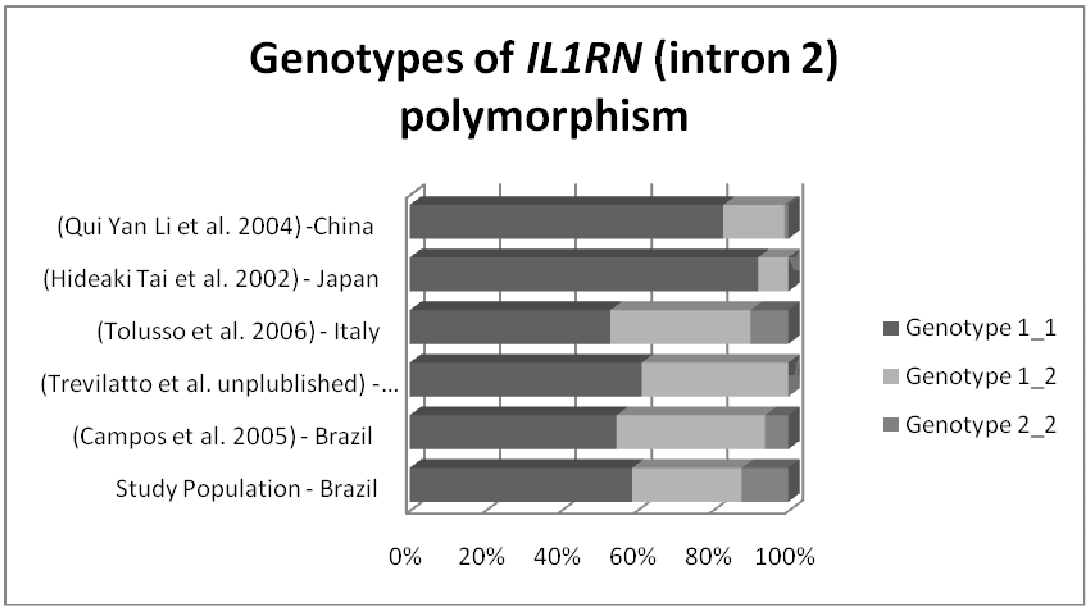


Figure 2. Genotype/allele frequencies of *IL1RN* (intron 2) polymorphism in different populations.





CONCLUSÃO

5. Conclusão

i. Em estudo retrospectivo, os seguintes parâmetros foram associados à perda de implantes dentais osseointegráveis: sexo e região de colocação do implante. A maioria dos pacientes não apresentou causa clínica aparente para a perda de implantes, sugerindo que fatores do hospedeiro possam estar contribuindo para um maior risco à perda de implantes.

ii. Em estudo transversal, alelos e genótipos dos polimorfismos *IL1B* (C+3954T) e *IL1RN* (íntron 2) não estiveram associados à perda de implantes dentais osseointegráveis. Porém, parâmetros clínicos como: edentulismo, profundidade de bolsa e número de dentes presentes, mostraram-se relacionados à perda de implantes dentais osseointegráveis

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6. REFERÊNCIAS

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ANEXO

ANEXO:

Outros artigos relacionados à tese submetidos à publicação:

GENETIC SUSCEPTIBILITY TO DENTAL IMPLANT FAILURE: A CRITICAL REVIEW

Fabiano Alvim Pereira [1], Claudia C. Montes [1], Marcelo T. Mira, PhD[2], Paula C Trevilatto, PhD[2]

ANALYSIS OF ASSOCIATION OF CLINICAL ASPECTS AND VDR GENE POLYMORPHISM WITH DENTAL IMPLANT FAILURE

Alvim-Pereira F., Montes C.C., Thomé G., Menezes E., Olandoski M., Trevilatto P.C.

GENETIC SUSCEPTIBILITY TO DENTAL IMPLANT FAILURE: A CRITICAL REVIEW

Fabiano Alvim Pereira [1], Claudia C. Montes [1], Marcelo T. Mira, PhD[2], Paula C Trevilatto, PhD[2]

Abstract The observation that clinical factors alone do not explain why some patients develop implant loss, the understanding of the osseointegrated implant failure as a complex, multifactorial process and the observed aggregation of repetitive failure in certain individuals raise interesting questions related to host susceptibility to dental implant failure. Genetic analysis applied to dental implants began in the late 90's and since then, increased interest in genetic susceptibility to the phenotype has been demonstrated by several studies. These studies, however, have been based on and limited to candidate gene association analysis, intended to find association between specific alleles and/or genotypes of genetic markers and susceptibility to implant failure. The aim of this review is to provide a brief description of the current methodology for genetic analysis of complex traits, followed by a comprehensive review of the literature related to genetic susceptibility to dental implant failure and a discussion of different aspects of the applied methodology. Moreover, it brings up a novel approach of *genome wide, case-control analysis*, as an alternative method to access genetic influence to dental implant failure mechanisms. Advances towards the elucidation of the genetic basis of dental implant loss may contribute to the understanding of why some patients do not respond to currently available treatments while others do, providing potential targets for effective screening, prevention and treatment. For example, clinicians might be able to estimate, before the elective surgical procedure, the risk of a given patient to develop a negative individual host response.

ANALYSIS OF ASSOCIATION OF CLINICAL ASPECTS AND VDR GENE POLYMORPHISM WITH DENTAL IMPLANT FAILURE

Alvim-Pereira F., Montes C.C., Thomé G., Menezes E., Olandoski M., Trevilatto P.C.

Abstract: Osseointegration failure is a complex, multifactorial trait shown to concentrate in some treated populations. There have been shown some evidence for genetic contribution to dental implant failure. Genetic polymorphisms have been classically considered genetic risk factors for several diseases and, more recently, for dental implant loss. The purpose of this study was access clinical factors related to failure process and investigate the possible relationship between (rs731236, T*aq*I) VDR polymorphism and dental implant loss. Two hundred seventeen unrelated patients, mean age 51.7±11.3 years, were divided into two groups: *Control group (C)*, 137 individuals presenting at least one osseointegrated implant in function six months or more and without any implant failure, and *Study group (S)*, 80 individuals presenting at least one implant loss. After DNA collection and purification, VDR T*aq*I polymorphism analysis was performed by PCR-RFLP. Differences between control and study groups and between healthy (H; n=1232) and lost (L; n=135) implants were accessed. Regarding clinical aspects, the following parameters were observed to influence implant failure: edentulism, probing pocket depth, implant position, primary stability, and implant length. Cox Regression model showed that primary stability, surgery technique and bone quantity were related to implant survival over time. No association between genotypes or alleles of T*aq*I polymorphism and implant loss was found between the groups. It was concluded that clinical aspects, but not the study polymorphism, were associated with implant dental failure.