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DENTAL IMPLANT PROSTHODONTIC REHABILITATION AND IL-1 GENE POLYMORPHISMS

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ABSTRACT

The use of dental implants by dentists for oral rehabilitation has assumed a growing importance given the evolution and diversity of implant systems. However, it is still an area that raises some doubts in understanding some phenomena of implant failure and unsuccessful prosthodontics rehabilitation, which at first sight are inexplicable and unpredictable. In order to investigate a possible relationship between the interleukin-1 (*IL1*) gene polymorphisms (positions -889*IL1A* and +3953*IL1B*) and possible risk factors of unsuccessful dental implant prosthodontic rehabilitation it was conducted a study in a target population of 200 Caucasian patients rehabilitated with dental implants by using a genetic test (CGC Genetics, Portugal).

It was found a statistically significant association between the result (success and no success of the dental implant prosthodontic rehabilitation) and the presence of fixed prosthodontic rehabilitation of the natural teeth in the maxilla ($\chi 2$ = 7.036, df = 2, p <0.05).

Keywords: dental implants, no success, prosthodontics, IL-1 gene polymorphisms.

INTRODUCTION

For several years dental implant success criteria were mainly focused on the implant itself, not being taken into account the issues related to prosthetic rehabilitation and patient satisfaction (Albrektsson, 1986).The fact is that the Albrektsson criteria proposed in 1986 (Albrektsson, 1986) had a great impact on implantology therapies. These were considered the Gold Standard in implant success for several years. However, the wide range of the existing implant systems and the increasing attention in relation to aesthetics, among other aspects as the function, do not allow the widespread applicability of these criteria to all systems - so its update became imperative (Salvi & Lang, 2004; Schwartz-Arad, 2005; Elkhoury, 2005; Sunitha, 2008; Misch, 2008; Papaspyridakos, 2012).

The implantologists and prosthodontists must follow a more extensive implant success criteria, with specific indexes for endosseous implants that also contemplate aesthetics, function and prosthodontics, not considered before (Misch, 2008; Lang, 2012; Papaspyridakos, 2012).

In most cases, implant-supported or implant-retained treatments provide predictable results with improved stability, retention, aesthetics and patient satisfaction (Vaz, 2012).

The evolution and diversity of implantologic systems triggered the cumulative use of dental implants in oral prosthodontic rehabilitation and also their increasing success rate.

The success, durability and functionality of the prosthodontic rehabilitation with dental implants are the goal that every oral professional wants to achieve. Despite this, there still remain some cases that raise doubts in understanding implant failure phenomena and unsuccessful prosthodontics rehabilitation, which at first sight are inexplicable and unpredictable. In addition to that, the understanding of the osseointegrated implant failure as a multifactorial process and the clinical observation of repetitive unsuccessful dental implants in certain individuals raise interesting questions related to host susceptibility to failed dental implants (Vaz, 2012). So, the awareness that the implant loss tends to cluster in specific groups of individuals may suggest that host immune-inflammatory response can have a genetic basis (Montes, 2009; Dirschnabel, 2011; Vaz, 2012).

The peri-implant disease in patients rehabilitated with prostheses on dental implants is initiated by a host inflammatory response due to the presence of certain bacteria that colonize the peri-implant sulcus. Initially, this peri-implant disease is expressed by the peri-mucositis, which is a reversible inflammation of soft tissues surrounding the dental implant. This pathology may progress to a chronic condition – peri-implantitis - characterized by bone destruction around the dental implant (Lang, 1997; Klokkevold & Newman, 2000; Heitz-Mayfield, 2008).

The microflora of the gingival sulcus, in cases of chronic periodontitis, is similar to the one present in situations of peri-implantitis (Alcoforado, 1991; Heydenrijk, 2002; Pye, 2009). So, some authors believe that the progression of the host inflammatory response is analogous in both pathologies. Moreover, other investigations also refer that this response is controlled by specific genes, which define the type of response – protective or destructive (Malo & Skamene, 1994; LeSouëf, 2000; Woo, 2000; Taba, 2005).Furthermore, the basis of the host response type may be determined by the production of various cytokines (D'Aiuto, 2004), of which the interleukin-1(IL1) can be highlighted. The latter is controlled by three genes - *IL1A*, *IL1B* and *IL1RN* (Nicklin, 1994).

The presence of specific variations (polymorphisms) in genes *IL1A* and *IL1B* has been described by several authors as a risk factor forthe development and progression of periodontal disease (Kornman, 1997; McGuire & Nunn, 1999; Cullinan, 2001; Laine, 2001; Persson, 2003; Li, 2004; Lopez, 2005; Guzeldemir, 2008). In addition to this, some investigations refer that the genetic susceptibility to the pathology of the gingival sulcus can be assessed by a test, which determines the presence of polymorphisms in genes *IL1A* and *IL1B* (Kornman,1997; McGuire & Nunn, 1999; Cafesse, 2002; Greenstein & Hart, 2002; Persson, 2003; Lopez, 2005).This kind of genetic test (TGP® – genetic test for periodontitis - CGC Genetics, Portugal) performs the combined detection of two polymorphisms in *IL1A* and *IL1B* genes and has the assumption that positive genotype patients (with the presence of the two polymorphisms) have an excessive production of inflammatory cytokines in the gingival sulcus, especially Interleukin-1, and therefore lead to bone resorption (Kornman, 1999; McGuire & Nunn, 1999). So, this test is considered positive, if both alleles 2 are present in the two evaluated genes (*IL1A* and *IL1B*), which means that there is a substitution of a thymine by a cytosine.

Some authors have also studied the role of some genes and their variants (polymorphisms) in host responses in peri-implant biological complications and its progression (Wilson & Nunn, 1999; Rogers, 2002; Feloutzis, 2003; Shimpuku, 2003; Gruica, 2004; Campos, 2005; Jansson, 2005; Laine, 2006; Lachmann, 2007; Lin, 2007; Montes, 2009; Dirschnabel, 2011; Gurol,

2011; Hamdy & Ebrahem, 2011; Melo 2012, Vaz, 2012; Pigossi, 2012). Nevertheless, the role of *IL1* polymorphisms and of the TGP® and analogous tests, in determining success or failure of dental implants, has not been clarified yet. There still remains some doubts and controversy (Greenstein & Hart, 2002; Laine, 2006; Lachmann, 2007; Andreiotelli, 2008; Huynh-Ba, 2008; Nowzari, 2008; Dereka, 2012).

The aim of this study was trying to determine the existence of a relationship between the success and the no success of prosthodontic rehabilitation, alleles of IL1 gene (positions -889*IL1A* gene and +3953*IL1B* gene) and the type of oral prosthetic rehabilitation in Caucasian patients rehabilitated with at least one dental implant.

MATERIAL AND METHODS

This research followed the international legal norms (Helsinki Declaration) and was accepted by Ethical Committee of the Dental Medicine Faculty of University of Porto (Portugal). So, all the participants signed an informed consent.

The study was conducted in a target population of 200 Caucasian patients rehabilitated with at least one dental implant and with a good general health condition. 45 subjects were removed by impossibility of obtaining all necessary information. The final sample consisted of 155 patients. The sample size complied with the existing literature regarding the rate of dental implant failure (about 10%) (Buser, 1997; Misch, 2008; Ormianer & Palti 2008; Mangano, 2009), with an estimation error of 5% and a confidence interval at 95%. So, the calculated minimum sample size required for this study was of 139 patients, but 155 subjects were evaluated (working with an error of around 4.8% and a 95% confidence interval). The 155 patients were separated into two groups: Group A - patients rehabilitated with dental implants with no success, Group B -patients successfully rehabilitated with dental implants.

The criteria of no success were adapted to the published literature (Gruica, 2004; Salvi & Lang 2004; Misch, 2008; Mangano, 2009) and included: implant failure (implant loss after osseointegration), development of any biological complications – mobility, pain on palpation, percussion or function; recurrent infection (fistula or suppuration); peri-mucositis; peri-implantitis; and vestibular metal exposing during or after the abutment connection.

All the participants in this study answered an inquiry about personal data; family clinical history; general and oral health; medication; alcohol, smoking and other toxic habits. The subjects also performed a clinical examination involving implant assay, occlusion analysis and prosthodontic evaluation. The prosthodontic evaluation focused on all kinds of alternative prosthetic rehabilitation: removable and fixed on natural teeth, on the mucosa, or by implants. The material of fixed and removable prosthetic rehabilitation was also recorded.

All the patients that participated in this study were rehabilitated with dental implants by clinicians with a minimum of 10 years of professional training as Implantologist/ Oral surgeon/Periodontologist/Prosthodontist dentists. It was also ensured that all patients were evaluated after implant surgery, delivering the prosthesis, control maintenance (with instruction and monitoring of proper oral hygiene), and that all patients had been recalled annually.

The exclusion criteria were: history of chronic illness, HIV infection, current pregnancy or lactation, orthodontic appliances and periodontitis at the moment of observation.

Biological material for the genetic test was obtained through a bucal swab of every patient that participated in the study. The TGP® test performs a combined molecular detection of

polymorphisms in *IL1A* and *IL1B* genes (positions -889 and +3953) and it is based on reverse hybridization technology on strips of cellulose - DNA Strip ®. This test is divided into 3 laboratorial stages: isolation of DNA sample from each patient, a multiplex PCR amplification and a reverse hybridization (Fig. 1).

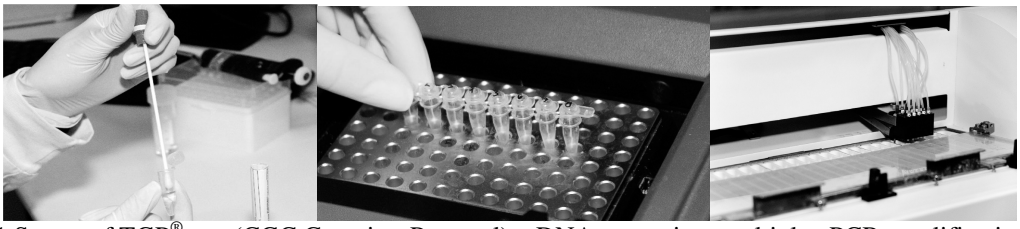


Fig. 1 Stages of TGP® test (CGC Genetics, Portugal) – DNA extraction, multiplex PCR amplification and reverse hybridization

The evaluation of TGP® results is made on cellulose strips. Each strip has eight zones of reaction: conjugate control (CC), specificity control (Spec-C), sensitivity control IL1A-889 (Sens-IL1A), IL1A-C889, IL1A-889T, sensitivity control of IL1B+3953 (Sens-IL1B), IL1B+C3953 and IL1B+3953T (Fig. 2).

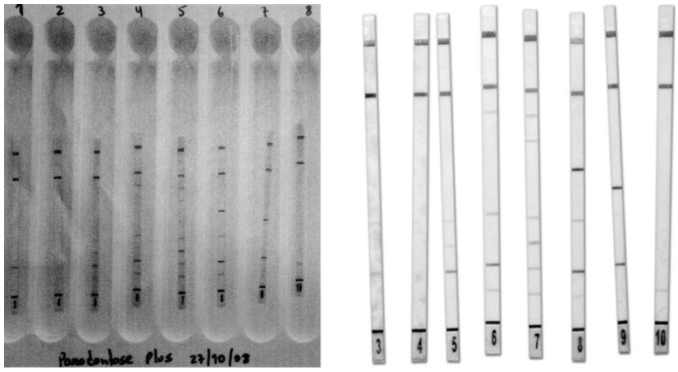


Fig. 2 Evaluation of TGP® results on cellulose strips

The collected data were analyzed with SPSS 20.0®. Given the nature of the variables involved, the analysis consisted of descriptive and analytical study of data.

The independence chi-square test, 2x2 tables and the exact Fisher test were used in the analytical data evaluation.

In addition to the mentioned descriptive and analytical study, we used analysis techniques resorting to modeling by means of a binary logistic regression. The aim was to evaluate the odds ratio in the presence or absence of a particular risk factor.

The adopted decision rule consists of detecting a significant statistical evidence for probability values (proof test value) of less than 0.05.

In a clinical sense, risk factor is understood as being a characteristic that predisposes an individual to any kind of disease. In epidemiological language, it can be interpreted as an independent variable (cause) likely to modify a dependent variable (effect).

RESULTS AND DISCUSSION

The final sample size of this study consisted of 155 individuals- 100 cases matching the success of prosthodontics rehabilitation with dental implants and 55 cases with no success, which accounted for 64.5 percentage success cases and the remaining 35.5 to no success cases (Fig. 3).

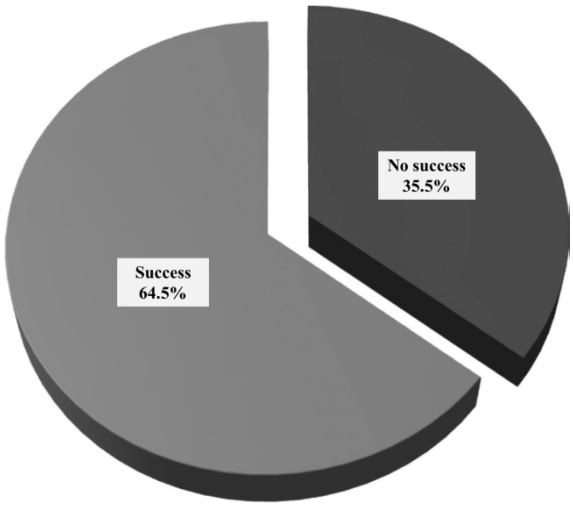
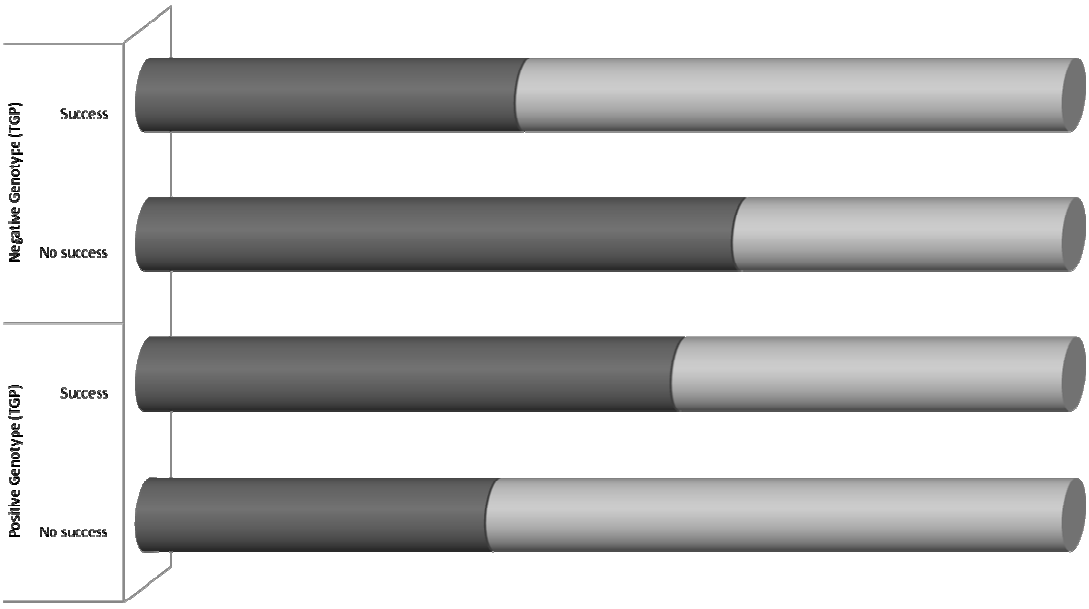


Fig. 3 The percentage of cases of success and no success of the prosthodontic rehabilitation with dental implants on the sample

The patients' ages of the sample ranged between 21 and 78. These results obtained in relation to the size and variation age are consistent with the published literature similar to our study (Wilson & Nunn, 1999; Rogers, 2002; Shimpuku, 2003; Feloutzis, 2003; Laine, 2006).

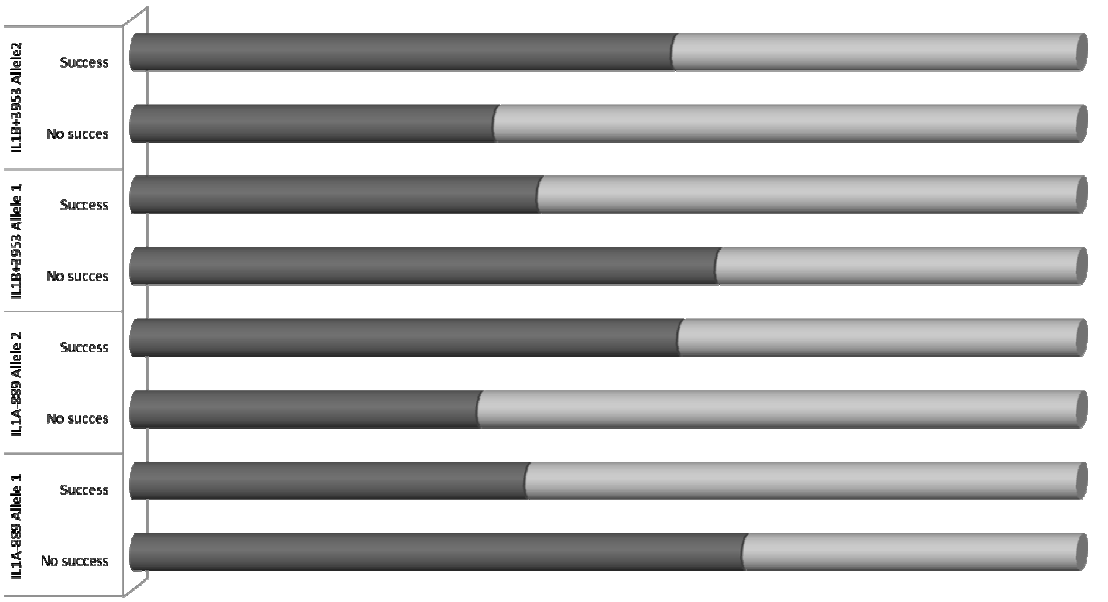
Although the differences were not statistically significant, the positive *IL1* genotype (positive TGP® result) showed a tendency to be more associated with the no success and negative *IL1* genotype (negative TGP® result) was found to be more related to the success of the prosthodontic rehabilitation with dental implants (Fig. 4).

The same behavior in the sample was also found for the alleles 2 of the two studied genes (*IL1A* and *IL1B*) - the no success was more associated to the presence of allele 2 of *IL1B* gene and allele 2 of the *IL1A* gene (Fig. 5). These results are in accordance with similar literature (Wilson & Nunn, 1999; Rogers, 2002; Gruica, 2004; Jansson, 2005).



	Positive Genotype (TGP)		Negative Genotype (TGP)	
	No success	Success	No success	Success
Not has	29,1%	70,9%	50,0%	50,0%
Has	48,1%	51,9%	27,7%	72,3%

Fig. 4 Distribution of TGP® results and successful or unsuccessful cases on the sample



	IL1A-889 Allele 1		IL1A-889 Allele 2		IL1B+3953 Allele 1		IL1B+3953 Allele2	
	No success	Success	No succes	Success	No succes	Success	No succes	Success
Not has	47,1%	52,9%	26,7%	73,3%	46,6%	53,4%	28,9%	71,1%
Has	25,9%	74,1%	46,4%	53,6%	28,9%	71,1%	46,6%	53,4%

Fig. 5 Allelic composition (alleles 1 and 2 of IL1A and IL1B genes) of the sample

As illustrated in Fig. 6 we could verify that the prosthodontic rehabilitation fixed on natural teeth in the maxilla, both in the metal-ceramic as the ceramic materials, had a larger number

of successful cases. After being performed, the chi-square test proved the existence of a statistically significant association between the result (success or no success of the prosthodontic rehabilitation with dental implants) and the presence of fixed prosthodontic rehabilitation on natural teeth in the maxilla ($\chi 2 = 7036$, df = 2, $p < 0.05$).

The same did not happen for the mandible - it was not found a significant statistical association between the presence of fixed prosthodontic rehabilitation on natural teeth in the mandible and the success or no success of the prosthodontic rehabilitation with dental implants (Fig. 7).

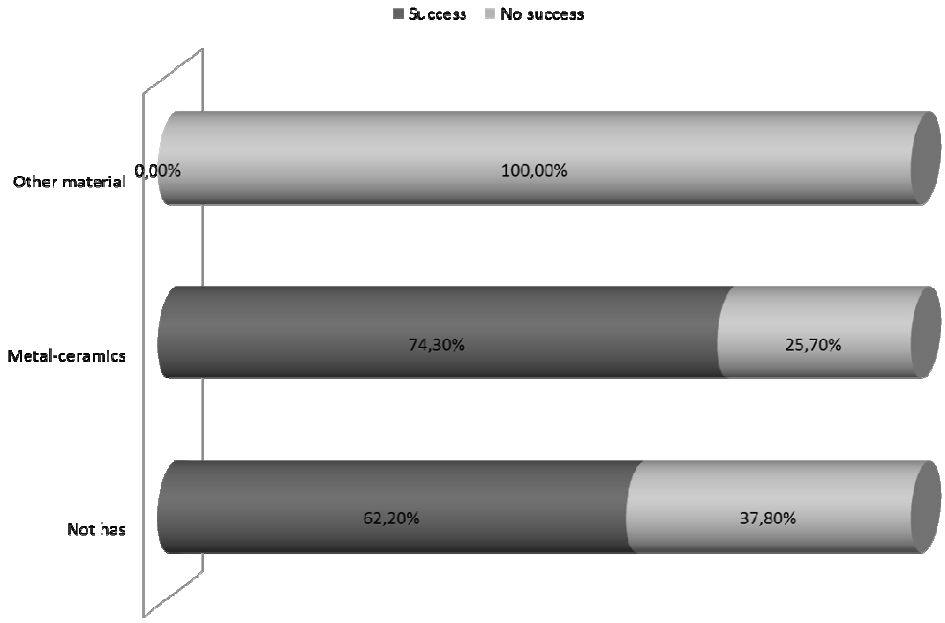


Fig. 6 Distribution of fixed prosthodontic rehabilitation on natural teeth in the maxilla by the result (success or no success of the prosthodontic rehabilitation with dental implants)

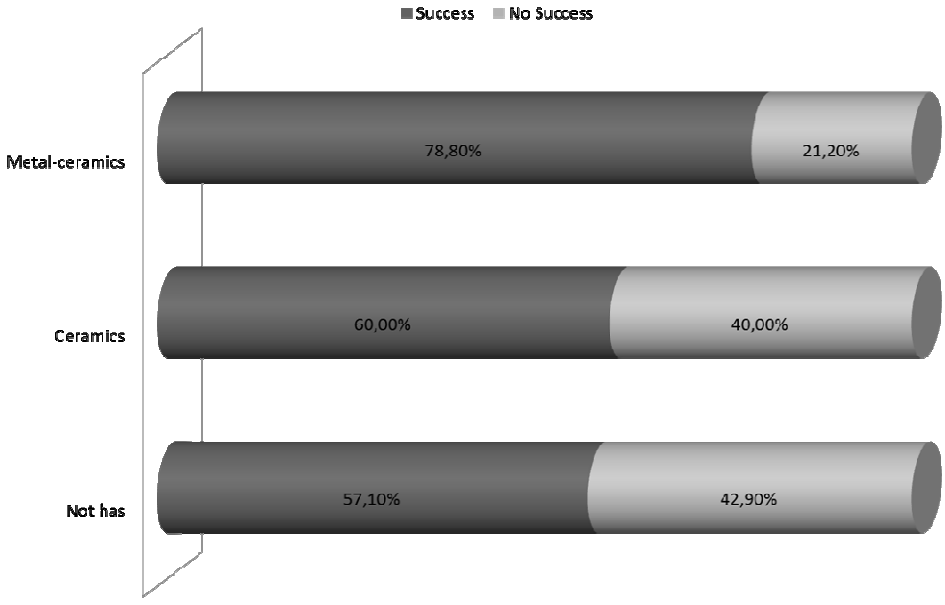


Fig. 7 Distribution of fixed prosthodontic rehabilitation on natural teeth in the mandible by the result (success or no success of the prosthodontics rehabilitation with dental implants)

The main similar studies cannot be compared to ours neither on the parameter prosthodontic rehabilitation nor on the result (success or no success of prosthodontic rehabilitation with dental implants). These studies either did the previous selection of the patients with the same prosthodontic rehabilitation with dental implants (Gruica, 2004), or did not contemplate the type of prosthodontic rehabilitation with dental implants(Wilson & Nunn, 1999; Shimpuku, 2003; Campos, 2005; Jansson, 2005), or showed a healthy control group without prosthodontic rehabilitation with dental implants (Rogers, 2002) or even considered the no success group as only a biologic complication (such as peri-implantitis, implant loss or peri-implant bone loss) (Wilson & Nunn, 1999; Hamdy & Ebrahem, 2001; Shimpuku, 2003; Lachmann, 2007; Montes, 2009).

CONCLUSION

The authors that have made studies of a similar nature to ours did not refer any information about the type of prosthodontic rehabilitation with dental implants or even the data about the other types of oral prosthodontic rehabilitations.

We can conclude that further studies are needed to relate the success or no success of prosthodontics rehabilitation with dental implants to the presence of prosthodontic rehabilitations fixed on natural teeth as well as the materials and the type of removable prostodontic rehabilitation and the TGP® genotype and the alleles present for *IL1* and other gene polymorphisms.

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