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Outcome of orthodontic mini-implant loss in relation to interleukin 6 polymorphisms

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Abstract. Mini-implants (MIs) are used increasingly for orthodontic anchorage and their success may require some osseointegration, which is affected by the underlying host immune-inflammatory response. Interleukin 6 (IL-6) is a cytokine expressed during the host response after a trauma or infection. The aim of this study was to investigate the association of clinical characteristics and *IL6* tag single nucleotide polymorphisms (which capture the information of the whole gene in terms of genetic variability) with the loss of MIs for orthodontic anchorage. A total of 487 patients were treated with orthodontic MIs between 2004 and 2010. After the application of inclusion and exclusion criteria, the sample comprised 104 patients with one or more MIs that had been in function for at least 6 months with no loss, and 31 patients who had lost one or more MIs. Allele A of rs2069843 and allele T of rs2069849 were suggestively associated with the loss of MIs for orthodontic anchorage and were in complete linkage disequilibrium, which means that one of them is sufficient to capture the same information. The location of installation (mandible) and the number of MIs installed per patient were also associated with the loss of MIs.

Key words: mini-implants; mini-implant loss; clinical risk factors; polymorphisms; *IL6*.

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Anchorage is defined as a 'resistance to unwanted tooth movement'. Traditionally, orthodontists have used teeth, intraoral appliances, and extraoral devices to guarantee adequate anchorage, thereby minimizing the movement of certain teeth while completing the desired movement of others. However, because of Newton's third law, ''for every action there is an equal and opposite reaction'', there are limitations in our ability to completely control all aspects of tooth movement; moreover, this will depend on patient compliance.[1] Good anchorage control is a prerequisite to successful orthodontic therapy.

Implants are currently used in dentistry and orthopaedics. The possibility of orthodontic anchorage using implants was proposed in 1945,[2] but the biological basis for osseointegration was provided by the pioneering work of Brånemark et al.[3] Dental endosseous implants have since been used successfully in clinical practice for replacing missing teeth and for orthodontic anchorage.

The clinical advantages of skeletal anchorage over dental and extraoral anchorage are the absolute stability and the independence from patient compliance.[4]

Skeletal anchorage has included onplants, osseointegrated implants in the palatine suture, zygomatic ligatures, mini-plates, and mini-implants.[5]

Mini-implants (MIs) were introduced as a simple alternative for orthodontic anchorage.[5] Advantages are that they are small, can be used at a variety of host sites, insertion is a minimally traumatic procedure, and they can be loaded immediately.[6] Other advantages include their ability to withstand orthodontic forces, applicability to any type of treatment, including interceptive therapy, the shorter treatment time with no need to prepare dental anchorage, the fact that they do not require compliance, and that they are biocompatible, low cost,[7] and can be used to maintain an edentulous space after active orthodontic treatment.[8]

Osseointegration can occur around screws and stabilization can be maintained, even under early loading.[9] Histological studies in animals have shown that osseointegration of titanium MIs is less than half that of conventional dental implants.[6] Incomplete osseointegration represents a distinct advantage in orthodontic applications, allowing effective anchorage with easy insertion and removal.[10] MIs used as orthodontic anchorage should be loaded early to reduce the treatment time and should be removed after treatment.[4] Immediate loading does not inhibit the osseointegration of MIs but stimulates bone adaptation.[9]

Inflammation surrounding implants is a crucial pathophysiological process that allows the elimination of local tissue damage and substitution with a viable tissue. The augmentation of the inflammatory process is directly related to the quantity of tissue that may be substituted.[11] Complete stabilization between pins and the surrounding bone is required to achieve a successful osseointegration. After the bone regeneration process, stability reaches the maximum value when osseointegration is achieved.

Interleukin 6 (IL-6) is a 26-kDa pleotropic inflammatory cytokine produced by many cell types, including fibroblasts, monocytes, adipocytes, and endothelial cells. Characterization of IL-6 has revealed a multifunctional cytokine that is involved not only in immune responses, but also in haematopoiesis, inflammation, and bone metabolism. In addition, this cytokine acts synergistically with IL-1β, inducing bone resorption.[12] Moreover, IL-6 makes significant contributions to autoimmune and inflammatory diseases such as rheumatoid arthritis,[13] endothelial damage and initiation of an atherosclerotic event,[14] chronic anaemia,[15] gingivitis, and periodontitis.[16] The understanding of IL-6 gained has paved the way for new therapeutic approaches to autoimmune and inflammatory diseases.[13]

Polymorphisms are gene sequence variations with a minimum allele frequency higher than 1% in the population and are distributed throughout the entire genome[17]; these result in differences among people in terms of the modulation of susceptibility to certain diseases. Single nucleotide polymorphisms (SNPs) are the most common form of DNA variation in the human genome. In the present research, a novel genetic approach was used – genotyping tag SNPs. These are SNPs often highly linked to others by linkage disequilibrium (LD) forming a bin (a block with strong LD). Tag SNPs are representative of all other SNPs of a given bin, which reduces genotyping costs and time. Also, this physical strategy is intended to capture the information of the whole gene, further than single functional SNPs. The purpose of this study was to investigate the association of clinical characteristics and polymorphisms (tag SNPs) in the *IL6* gene with MI failure.

Materials and methods

Study population

A total of 487 patients were treated with orthodontic MIs (Neodent Implante Osteointegrável, Curitiba, Paraná, Brazil) at the dental research institute (ILAPEO) in Curitiba, PR, between 2004 and 2010, and these patient cases were examined by chart review. Of these 487 patients, 196 (40.2%) were included in the study (age 18 years or older, living in the metropolitan area of Curitiba, and agreed to participate in the study). After being advised of the nature of the study, 148 patients signed a consent form within a protocol approved by the institutional review board. Eight patients were excluded due to syphilis, current pregnancy, or lactation and five patients refused to participate in the study. The final study population comprised 135 subjects of both sexes, with a mean age of 48.7 ± 10, range 20–76 years (Table 1): the study group (S) consisted of 31 patients presenting at least one lost MI, and the control group (C) consisted of 104 patients without any MI lost, whose implants had been in function for at least 6 months.

Patients treated in ILAPEO are routinely asked to rinse with a 0.12% chlorhexidine solution preoperatively. No antibiotics were administered either before or after miniscrew placement. Patients in this study did not use non-steroidal anti-inflammatory drugs (NSAIDS) after implant placement.

The Brazilian population is heterogeneous. Recent articles have recommended against grouping Brazilians into ethnic groups based on colour, race, and geographical origin because Brazilian individuals classified as white or black have significantly overlapping genotypes, probably due to miscegenation.[18]

Subjects were recalled and answered questions on their personal, medical, and dental history. Their socioeconomic profile was also determined in accordance with the Brazilian Socioeconomic Classification Criteria of 2009.[19] The following variables were assessed: sex, age, smoking habits, socioeconomic status, general medical condition, use of medication, use of hormone replacement therapy, alcohol consumption, hygiene habits, the Decayed/Missing/Filled Teeth (DMFT) index, and the Community Periodontal Index of Treatment Needs (CPITN). The CPITN is a numerical rating scale for classifying the periodontal status of a person or population with a single figure, which takes into consideration the prevalence as well as the severity of the condition. It is based upon probe measurement of the periodontal pockets and on the gingival tissue status. The index was proposed by World Health Organization (WHO) in 1977 to evaluate the periodontal treatment needs of populations.[20] Periodontal indices were recorded in index teeth using a conventional University of North Carolina (UNC) periodontal probe (Hu-Friedy, Chicago, IL, USA). All clinical data were collected by one examiner (A.M.R).

Analysis of MI clinical parameters

The MIs used in the study patients were conical, titanium grade V, smooth-surfaced, self-drilling, and immediately loaded (Neodent Implante Osteointegrável). A total of 311 MIs were installed in the 135 patients (control and study group patients). Independent of the group, the MIs placed were classified as either healthy ($n = 272$) or lost ($n = 39$).

The following clinical characteristics were assessed and compared between healthy and lost MIs: location of installation (maxilla or mandible; vestibular, lingual, or alveolar ridge; right or left side), diameter, length, type of neck, type of anchorage, and type of movement.

DNA collection and purification

The study participants rinsed their mouths with mouthwash containing 5 ml