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Mechanobiology of Oral Implantable Devices

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1. Introduction

A dental implant is a biomaterial device inserted in the jaw bone to replace the root of a missing tooth Adell et al. (1981); Hansson et al. (1983). With the implant insertion, a junction site between the biomaterial surface and the surrounding bone known as the *bone-dental implant interface* is created Branemark (1983). The formation of a new bone matrix in this interface allows the firm and long lasting connection between the bone and the implant in a process called *osseointegration* Albrektsson & Johansson (2001); Branemark (1983). The success of this contact depends on the restoration of the functional tissues around the implant providing it with mechanical support and anchorage Gapski et al. (2003); Hansson et al. (1983). This tissue restoration is conditioned to cell migration, cell proliferation and cell differentiation phenomena depending on the pathological conditions of the patient, the biological conditions of the host bone, the implant design and surface topography, and the distribution of mechanical loads between the bone and the implant Aukhil (2000); Ellingsen et al. (2006); Sikavitsas et al. (2001). The analysis of both biological and mechanical factors is known as mechanobiology Klein-Nulend et al. (2005); Van der Meulen & Huiskes (2002).
Dental implants are widely used as anchorage devices for restoration and esthetical purposes Branemark (1983). However, in several orthodontic treatments where the anchorage is used, a higher control of treatment time and oral availability is needed Antoszewska et al. (2009); Gapski et al. (2003). In these cases, dental implants are not recommended since specific surgical procedures are required for their implantation usually demanding long lasting recovery times for insertion and loading Antoszewska et al. (2009). Furthermore, most of the orthodontic treatments are based on the temporary and direct application of loads for the movement of teeth Papadopoulos & Tarawneh (2007). This treatments rely on implantable devices capable of transmit immediate loading without the implicit need of being osseointegrated Papavasiliou (1996). Such devices, called mini-implants, reinforce the anchorage of orthodontic devices and speed up treatments given its relative simple insertion

procedure and lack of osseointegration Antoszewska et al. (2009); Papadopoulos & Tarawneh (2007); Papavasiliou (1996).
Although a bone-implant interface is also created around the inserted mini-implant, its mechanobiological behavior differs from that of the dental implants since mini-implants are not fully osseointegrated Antoszewska et al. (2009). This means that mechanical considerations as loading conditions, material and surface topography govern tissue recovery and bone formation around mini-implants. Therefore, failure of mini-implants is mostly related to anchorage mechanics as bone thickness, shape design, insertion angle and insertion forces Antoszewska et al. (2009); Gracco et al. (2009); Motoyoshi, Inaba, Ono, Ueno & Shimizu (2009a); Motoyoshi, Okazaki & Shimizu (2009).
The purpose of this chapter is to provide a review of dental implants and mini-implants from a mechanobiological approach. The aim is to present the influence of intrinsic biological and mechanical conditions leading to tissue recovery at the bone-implant interface. External loading, surface treatment and surgical procedures are also addressed as conditions for the success of both kinds of devices. The discussion is supported on a vast literature review of theoretical, clinical and experimental evidence. Self-conducted experiments based on tissue engineering techniques are presented for supporting ideas on the interaction of body components with biomaterials, and for the evaluation of their biocompatibility.
Finally, we suggest several guidelines for the mechanobiological modeling of the bone-implant interface. Although the healing processes at the bone-implant interface have been deeply discussed in the experimental literature, in recent years mathematical models have gain insight for their capacity of reproduce implants behavior. Several models describe the biological events leading to bone healing at the interface and many others describe the mechanical loading environment and the implant surface interactions under the assumption of partially or even fully osseointegrated interfaces. For the modeling guidelines, we present a brief discussion of these models and comment on ways for the formulation of experimental procedures for obtaining numerical parameters used in the models, and for the qualitative and quantitative validation of the numerical results.

2. Dental implants

2.1 The bone-dental implant interface

Teeth are anatomic structures used during chewing. Each tooth has a crown, a neck and a root Lang et al. (2003); Lindhe et al. (2003). The crown is the visible part inside the mouth while the root lies inside the jaw bone. The neck is the boundary between the crown and the root Lindhe et al. (2003). Teeth are positioned in the jaw bone through the so-called *dental alveoli*, a type of sockets formed directly inside the *alveolar bone*.
A dental implant is a biomaterial device surgically inserted in the jaw bone to replace the root of a missing tooth Adell et al. (1981); Hansson et al. (1983). The implant is part of the prosthetic unit that replaces the missing tooth and that compromises the abutment, the joint and the prosthesis that finally replaces the lost crown (Figure 1).
There are several types of dental implants although the most recognized are those with a roughed and screwed body with dimensions ranging from 6.0 mm to 16.0 mm length and 3.5 mm to 5.0 mm diameter, depending of the kind of missing tooth Branemark (1983); Gapski et al. (2003). However, the optimal length and diameter needed for a successful long lasting implantation depends on the anchorage conditions of the host bone, and the biological and mechanical factors associated to bone healing Aukhil (2000); Davies (2003);

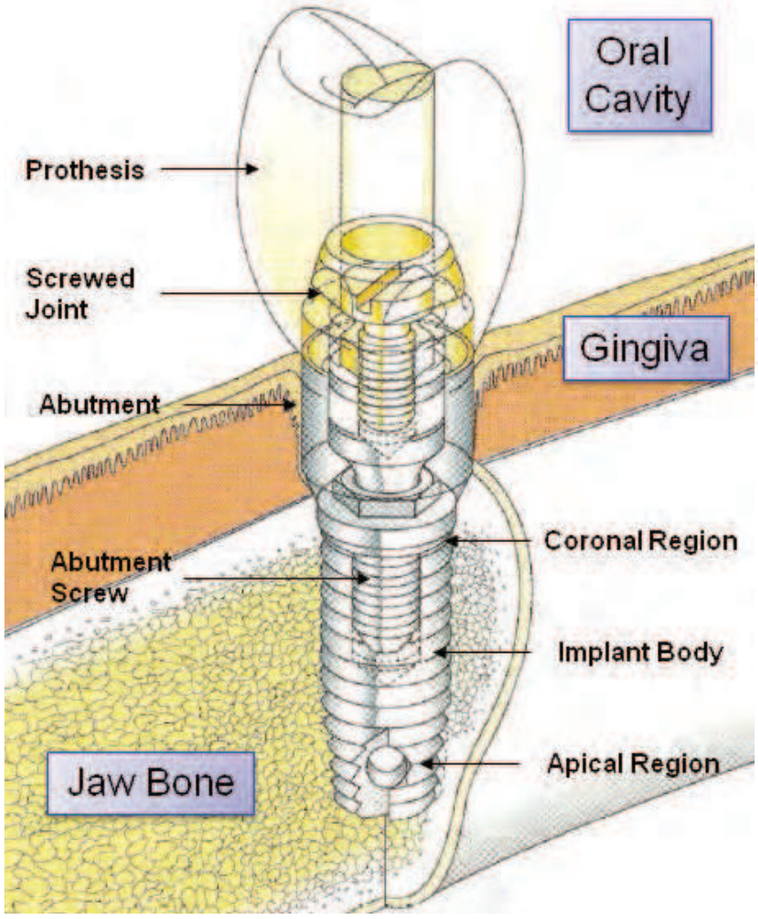

Fig. 1. Detail of a screw-type dental implant. Adapted from Aparicio (2005).

Gapski et al. (2003); Häkkinen et al. (2000); Klein-Nulend et al. (2005); Sikavitsas et al. (2001). There are nowadays different geometries of dental implants available although the most known is the screw-type geometry introduced in the 1960's by PI Branemark Branemark et al. (1969). This type of implant shows high mechanical retention provided by its canalled body, its outstanding ability in transferring compressive forces, and its improved primary stability capability Gapski et al. (2003); Martínez et al. (2002).

Most of the currently commercial dental implants are made of commercially pure titanium Adell et al. (1970) due to its proven biocompatibility, i.e., its acceptance by the living tissues Ellingsen et al. (2006); Ratner et al. (1996). The biocompatibility comprises the absence of corrosion and material wearing that may lead to undesirable inflammatory responses, death of surrounding tissues or thrombus formations by unexpected coagulation effects. It also implies for the living organism not to produce undesirable immunological responses such as an increase in antibody counting, cell mutations or formation of cancer cells Aparicio (2005); Hansson et al. (1983); Ratner et al. (1996).

Besides the implant characteristics, the insertion procedure has been shown to be of importance in the success of the prosthetic unit. The presence of a large number of bacteria inside the mouth demands the injury caused during implant placement to be carefully preserved in order to avoid possible infections leading to implant lost. According to this, the

most referenced insertion technique includes the implant coverage with the epithelial tissue originally present at the insertion site Branemark (1983); Branemark et al. (1969); Fragiskos & Alexandridis (2007); Gapski et al. (2003); Leckholm (2003); Lindhe et al. (2003).
The use of this technique reduces the wound healing time by the temporally isolation of the implant from an environment full of microorganism as the oral cavity and increases the bone formation at the implant surface reducing the bacterial contamination risk Branemark (1983); Gapski et al. (2003); Hansson et al. (1983). In general terms, this technique known as *two-stages* needs for two surgical interventions to complete the prosthesis placement Branemark et al. (1969). During the first intervention the implant is inserted in the placement site and covered by the epithelial tissue. 4 to 6 week later, a second intervention is carried out to remove the epithelium cover, expose the cortical side of the implant and attach the abutment and the prosthesis Fragiskos & Alexandridis (2007).
However, there is another type of insertion technique in which the implant, the abutment and the prosthesis are placed at the same time during a single surgical intervention. This technique known as *single-stage* avoids the epithelium coverage but reduces the healing time increasing then the patient benefit Heydenrijk et al. (2002). Nevertheless, this technique is less used due to bacterial contamination problems present during wound healing and an increased damage on growing tissues by micromovements caused during the earlier loading of the prosthesis and the implant Gapski et al. (2003); Heydenrijk et al. (2002).

2.2 Osseointegration

Although the evaluation of the anatomic characteristics of the host alveolar bone, the selection of the implant and the use of an adequate insertion protocol are conditions related to the bone-dental implant interface successfully healing, the implant osseointegration depends more on the bone formation directly over the implant surface Albrektsson & Johansson (2001); Branemark (1983). A successful osseointegration requires the action of two previous processes: *osteoinduction* and *osteoconduction* Albrektsson & Johansson (2001). Osteoinduction is the process by which stem cells are somehow stimulated to differentiate at the bone-dental implant interface into osteogenic cells that synthesize bone tissue (Figure 2a). New bone deposition by this cells is known as *osteogenesis* (Figure 2b) Albrektsson & Johansson (2001). There are two kinds of osteogenesis. A first *distant osteogenesis* where bone tissue is formed from the host bone border towards the implant surface Davies (2003), and a second *contact osteogenesis* where bone tissue is formed from the implant surface towards the host bone border (Figure 2b) Davies (2003); Puleo & Nanci (1999).
Contact osteogenesis implies the implant surface to be colonized by the osteogenic cells Davies (2003). This cell colonization or osteoconduction allows the bone growth over a biomaterial surface (Figure 2c) Albrektsson & Johansson (2001); Davies (2003). This process essentially depends on the material biocompatibility and the implant surface characteristics Huang et al. (2005); Wennerberg et al. (2003). Osteoconduction creates a direct contact between the implant and the surrounding growing tissues forming a contact interface that after the complete wound healing process conduces to the implant osseointegration (Figure 2d).
The canalled body of the screw-type dental implant allows it to support stresses and provide stability, while the deep surface irregularities provide the implant surface with a surface patter similar to that left behind by the osteoclasts after bone resorption during bone remodeling Martínez et al. (2002); Stanford & Schneider (2004). This surface pattern allows the osteogenic cells front to synthesize the first new bone line or *cementation line* interlaced with the

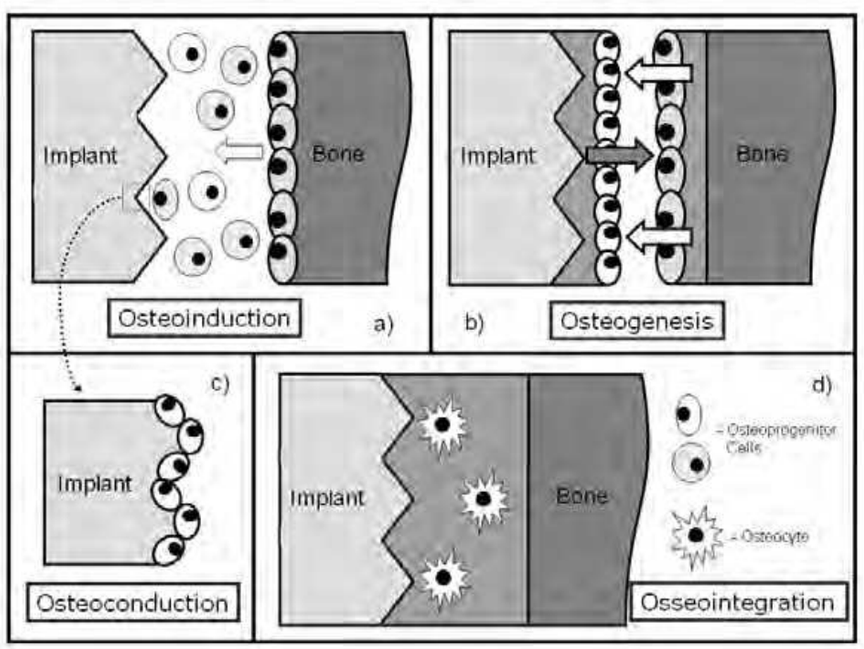

Fig. 2. Osteoinduction (a) is the osteogenic cells differentiation at the interface. Osteogenesis (b) is initiated by the osteogenic cells migrating from the host bone border (direct osteogenesis, white arrows) and by the osteogenic cells colonizing the implant surface (contact osteogenesis, gray arrow). Osteoconduction (c) is the surface colonization by the osteogenic cells. An adequate formation and bone viability (presence of osteocytes) surrounding the implant allows for a successful osseointegration (d) at the bone-dental implant interface.

irregularities, therefore ensuring an adequate new bone formation directly over the implant Davies (2007).

2.3 Mechanobiology of the bone-dental implant interface

Bone-dental implant interface healing consists of four biological stages each one associated with a characteristic biological event Aukhil (2000); Lang et al. (2003) (Figure 3): 1) hematoma formation (bleeding and blood clotting), 2) clot degradation and wound cleansing (fibrinolysis), 3) granulation tissue (fibroplasia and angiogenesis) formation, and 4) new osteoid formation (bone modeling).

Biological wound healing events are activated by bleeding during implant placement Fragiskos & Alexandridis (2007); Heydenrijk et al. (2002). The injured blood vessels initially become constricted and platelets from the bloodstream become activated to form a plug which temporarily stops blood loss Furie & Furie (2005); Minors (2007). Once activated, platelets aggregate and release granules containing several molecules that control the initial activity at the injured area, including platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-β) Gorkun et al. (1997); Minors (2007).

The temporary plug is later replaced by an hemostatic plug formed by a kinetic reaction between thrombin and fibrinogen, two proteins present in blood Furie & Furie (2005); Mann (2003). Thrombin converts fibrinogen into *fibrin fibers* Gorkun et al. (1997); Minors (2007).

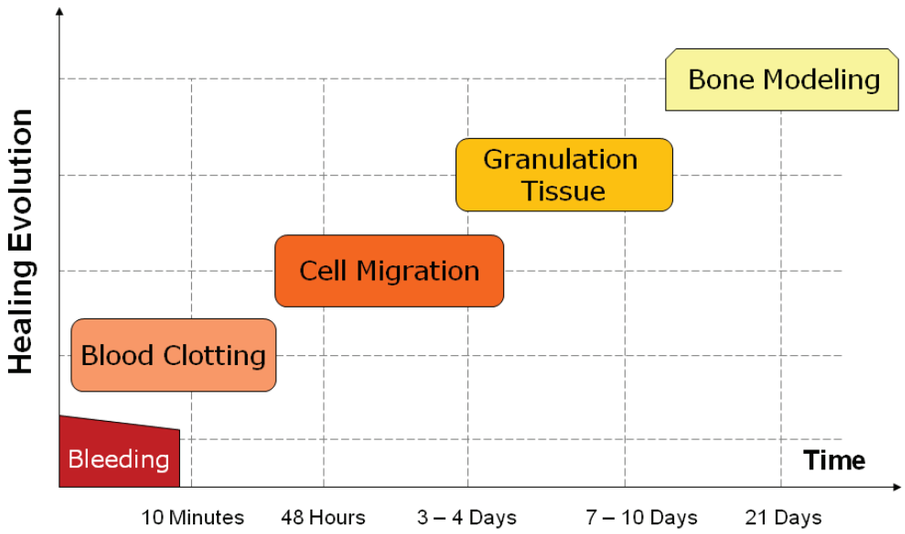

Fig. 3. Biological stages of healing at the bone-dental implant interface Ambard & Swider (2006); Dimitriou et al. (2005); Lang et al. (2003).

These fibers are accumulated to form the *fibrin clot* that completely detains blood flow and also protects tissues left exposed after implantation Aukhil (2000).
Some fibrin fibers are broken down after coagulation to allow the flow of stem cells responsible for restoring the tissues Collen & Lijnen (1991); Pasi (1999). Such degradation is accomplished by *plasmin*, a protein present in blood plasma in its inactive form known as *plasminogen* Aukhil (2000); Collen & Lijnen (1991); Li et al. (2003), and macrophage and neutrophil cleaning activity Davies (2003); Lang et al. (2003). Around the fourth day of healing, a process known as *fibroplasia* begins the replacement of the fibrin clot into a new extracellular matrix known as *granulation tissue* which mainly consist of collagen and new capillaries formed during angiogenesis Aukhil (2000). This new matrix supports the *osteogenic cells* migration Lang et al. (2003), stimulated by several molecules released during blood clotting and clot cleansing, such as PDGF, TGF-β Davies (2003) and fibroblast growth factor (FGF) Dimitriou et al. (2005).
Between the 7-10th day of healing, some of the fibroblasts present in the interface are transformed into *myoblasts* Häkkinen et al. (2000) characterized by smooth muscle *α-actin* cytoplasmatic microfilaments, allowing them to generate contractile forces responsible for wound contraction Aukhil (2000); Davies (2003); Häkkinen et al. (2000). *Osteogenesis* or new bone formation along the vascular structures is started Lang et al. (2003); Meyer & Wiesmann (2006) by day 14 after injury Dimitriou et al. (2005); Lang et al. (2003). Here, granulation tissue is replaced by new collagen fibers that are slowly mineralized to create the new bone matrix Meyer & Wiesmann (2006); Sikavitsas et al. (2001) by contact and direct osteogenesis Davies (2003).
Biological activity regarding wound healing at the bone-dental implant interface concludes with the modeling and subsequent bone remodeling Sikavitsas et al. (2001). Moreover, cell adhesion, cell migration and proliferation on surrounding tissues, and internal and external mechanical loads action modify the new tissue formation profile (Figure 4). Such phenomena may act as follows. First, the adhesion phenomena produced by cells fixation to a substrate Anselme (2000) activate chemical signaling Kasemo (2002) controlling cell proliferation and differentiation, as in platelet aggregation and activation stages Collen & Lijnen (1991).

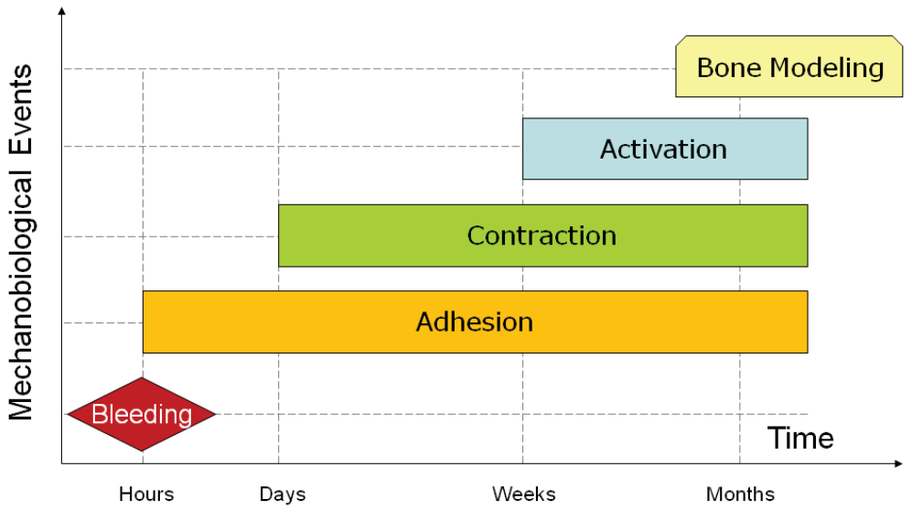

Fig. 4. Mechanical phenomena occurring during the healing of the bone-dental implant interface.

Then, the contraction exerted by cells moving over a substrate Häkkinen et al. (2000) may cause the displacement of the attached fibrin fibers and their detachment from the implant surface Davies (2003; 2007). This kind of event is present during fibroplasia and modeling stages where fibroblasts and osteogenic cells adhere to the fibrin network and begin to move through it in an attempt to colonize the implant surface. Fibers detachment prevents suitable bone formation directly over the implant surface and consequently increases the risk of implant rejection Adell et al. (1981); Branemark (1983).
Finally, the mechanical activation caused by applying an external load may induce the metabolic activity necessary for producing structural changes in the extracellular matrix of the tissues being formed Klein-Nulend et al. (2005); Sikavitsas et al. (2001). A phenomenon of this kind is particularly relevant during *bone mechanotransduction* Burger et al. (2005); Knothe-Tate (2003), which is responsible for controlling functional adaptation to external loads during modeling. Such mechanical adaptation exhibited by bone is widely known as *Wolf's Law* Sikavitsas et al. (2001); Stanford & Schneider (2004).

2.4 Experimental assays

Several studies have been carried out to evaluate the biocompatibility of different materials commonly used for dental implant manufacturing Matsuno et al. (2001); Metikos-Hukovic et al. (2003). It is well known that titanium is the best material of choice due to its high corrosion resistance to the physiological environment and its mechanical stability during the whole healing process Hansson et al. (1983); Watari et al. (2004). It also has been found that niobium, tantalum, zirconium, vanadium, aluminium and molybdenum are the most favourable materials to be used in titanium alloys for biomedical application Niinomi (2003). Although these alloys are non-toxic and highly inert Niinomi (2003); Watari et al. (2004), most of them do not establish a strong connection with the surrounding tissues and often induce the formation of fibrous tissue rather than bone tissue Ellingsen et al. (2006). This fibrous tissue provides inadequate support to the implant avoiding its surface to be colonized by the bony cells Huang et al. (2005). In order to avoid this, dental implant surfaces are modified by surface treatments that create micron and sub-micron scale patterns in the metal

surface. These patterns increase the retention of molecules released during the activation of the healing processes at the bone-dental implant interface which also increase the grade of tissues restoration Aukhil (2000); Davies (2007). In addition, the use of inorganic mineral coatings improves the osteogenic capacity of the raw metal surface providing it with an osteoconductive profile that resembles the bone resorption surfaces Davies (2007); Kasemo (2002).

An adequate surface morphology allows the osteogenic cells to adhere and proliferate over the implant surface Kasemo (2002) and to form mineral deposits that become the new bone formation sites Davies (2003); Sikavitsas et al. (2001). Therefore, the strategies that modify the implant surface lead to implants with better osteoinductive and osteoconductive responses and to higher rates of bone deposition that result in successful osseointegration Davies (2007). Here we present a self-conducted experimental analysis perfomed on four different types of dental implant surfaces. The aim is to evaluate cell adhesion and cell proliferation profiles using cell culture techniques. From these assays we obtained initial information about the behavior of each one of the surfaces under a physiological-like environment allowing us to determine which of them had better performance in terms of the osteoinductive and the osteoconductive properties.

For these experimental approach we used 120 Ti-6Al-4V substrates of 15 mm diameter and 2 mm thickness. The substrates were divided into four groups according to their surface morphology: (1) machined, (2) sand-blasted/acid-etching (SBAE) surface, (3) hydroxyapatite-tricalcium phosphate Ha/TCP active surface (TCP), and (4) TCP/acid-etching surface (TCP+acid). All substrates were supplied by MIS Technologies Ltda. (Shlomi, Israel). The substrates were produced by milling and turning machines. Machined surface was achieved by using a cutting and polishing device. SBAE surface roughness and micro geometry was achieved by surface blasting with large particles (300-400 μm size) of Al_2O_3 followed by etching with HCl/H_2SO_4. TCP surface was achieved by blasting HA/TCP particles 200-400 μm size. TCP+acid surface was achieved by blasting HA/TCP particles 200-400 μm size and cleaning with HNO_3. After manufacturing, substrates were sterilized by gamma-radiation and vacuum packed in a clean environment. Before being used in the experiments describe below, substrates were placed in 24-multiwell Costar plates (Costar Corp., Cambridge, MA, USA). The plates were kept under UV radiation for 12 hours and then autoclaved at 120řC for 6 hours.

Surface morphology characterization of each type of substrate was performed in two ways. First, a Zeiss Stemi SV11 stereozoom microscope with a 4x magnification lens was used. Using a Zeiss AxioCam MRC5 coupled-camera device, macrostructural 2.0 x 1.5 mm field of view images of the four surfaces were obtained. Second, microstructural images at the 10 μm scale were obtained for the four surfaces using a LEICA Stereo Scan 440 scanning electron microscopy (SEM) at 20 KV.

Osteoblastic cementoblastoma-derived cells were derived from a human cementoblastoma through the conventional explant technique and characterized as described elsewhere Arzate et al. (1998; 2002). Ethic considerations were followed as approved by the Internal Review Board of the School of Dentistry of the National University Autonomous of Mexico Arzate et al. (2002). Cells were cultured in 75 cm^2 cell culture flasks containing Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and antibiotic solution (100 μg/ml streptomycin and 100 U/ml penicillin) (Sigma Chemical Co., St. Louis, MO, USA). The cells were incubated in a 95% air and 5% CO_2 environment at 37 °C. Cells at the second passage were used for all the experimental procedures.

Cell adhesion assay was performed on three samples of each one of the four types of substrates. Cells were plated and incubated for 24 hours in 500 μl of culture medium at standard conditions, as described above. After incubation, unattached cells were washed off four times with clean water and the remaining cells were fixed and stained with 300 μl of a solution made of 0.1% toluidine blue and 3.5% paraformaldehyde Hayman et al. (1982); Rodil et al. (2003). After 24 hours at room temperature, 100 μl of the supernatant was used for optical absorption reading with an ELISA (Enzyme Linked Immune Sorbent Assay) micro-plate reader at 630 nm. In this technique, the number of attached cells is proportional to the absorbance of the experimental samples Rodil et al. (2003).

Cell proliferation assay was performed on three samples of each one of the four types of substrates. The proliferation of the osteoblastic cementoblastoma-derived cells was determined by the MTT assay. This assay is based on the ability of mitochondrial dehydrogenases to oxidize thiazol blue (MTT), a tetrazolium salt (3-[3, 5+dimethylthiazolyl-2-y] 2, 5-diphenyltetrazolium bromide), to an insoluble blue formazan product Rodil et al. (2003). Cells were plated as in the adhesion assay and incubated for 1, 2, 5, 6 and 7 days. Fresh medium and antibody (500 μl) were added to the cultures every day. After each term, cells were incubated with 60 μl MTT at 37řC for 4 hours. Then, the supernatant was removed and 250 μl of dimethyl sulfoxide (DMSO) was added to each well. After 30 minutes of incubation the absorbance was read at 570 nm. Since the generation of the blue product is proportional to the dehydrogenase activity, a decrease in absorbance at 570 nm provides a direct measurement of the proliferation rate Mosmann (1983).

Surface morphology of the four types of substrates was characterized using stereozoom microscope and SEM. Machined surface exhibited the radial evenly-spaced wave structures created during the cut and polishing manufacturing procedures (Figure 5A). SEM image shows the parallel undulated fashion of these structures at the micron-scale (Figure 5B). For the SBAE substrate, a granular fashion surface was observed (Figure 5C). At the micron-scale, these granules appeared as *peak and valley* surface structures due to the abrasion procedure used during manufacturing (Figure 5D). The stereozoom microscope did not reveal these structures but shows a grain-like surface. TCP surface exhibited micron-surface irregularities with edges and undercuts as in the SBAE surface (Figures 5E and 5F). TCP+acid showed the most dense micron-surface texture (Figures 5G and 5H). A dense grain-like surface was observed through stereozoom. Extensive surface irregularities also with edges and undercuts were observed in SEM.

Cell adhesion and proliferation assays were carried out to evaluate the initial interactions of the osteoblastic-like cells with the biomaterial surface. For the adhesion assay, adherent cells were evaluated 24 hours after plating. The results are shown in Figure 6 and are given in terms of the absorbance measured at 630 nm. There was statistical difference between all results ($p < 0.005$, 95% confidence interval). Adhesion of osteoblasts is favoured in both TCP and TCP+acid surfaces, exceeding in more than 4 and 5 times respectively the cell attachment with respect to the machined surface. This suggests a higher cell interaction due to the presence of edges and undercuts in the biomaterial surface. In counterpart, adhesion to poorly treated surfaces is much lower, revealing the significance of micron and sub-micron structures over the target surface.

Figure 7 shows the results for the proliferation assay carried out after 1, 2, 5, 6 and 7 days of culture. Values are expressed as the absorbance at 570 nm, which is directly proportional to the metabolic activity of the cells and inversely proportional to the toxicity of the material Rodil et al. (2004). As illustrated, all surfaces have a negative proliferation profile between days 1

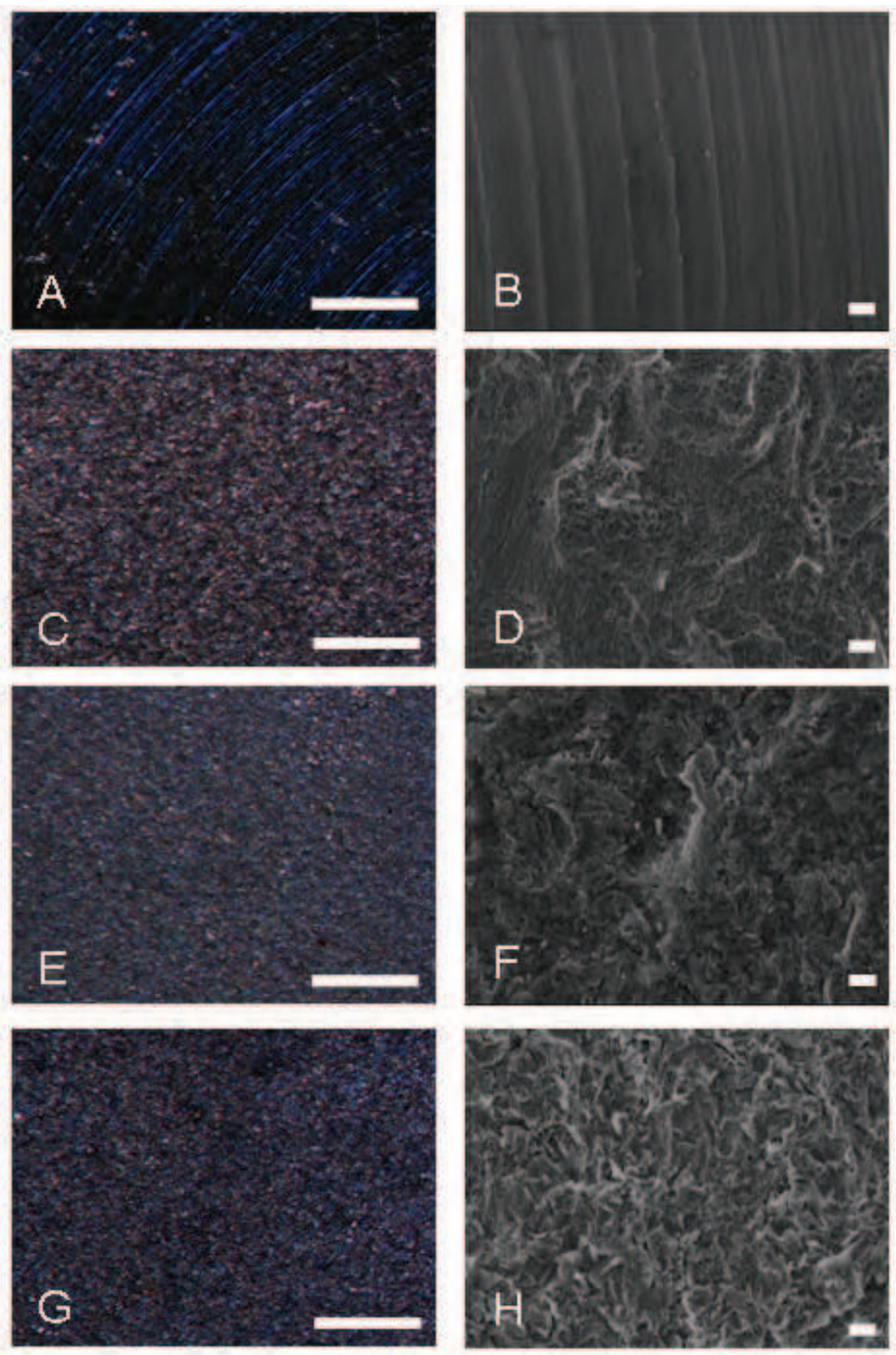

Fig. 5. Stereozoom and SEM micrographs of the four types of surfaces used in this study. Left, stereozoom microscopy (4x, bar = 0.5 mm). Right, SEM microscopy (2.500x, bar = 10 μm). (A) and (B) Machined surface, (C) and (D) SBAE surface, (E) and (F) TCP surface, (G) and (H) TCP+acid surface.

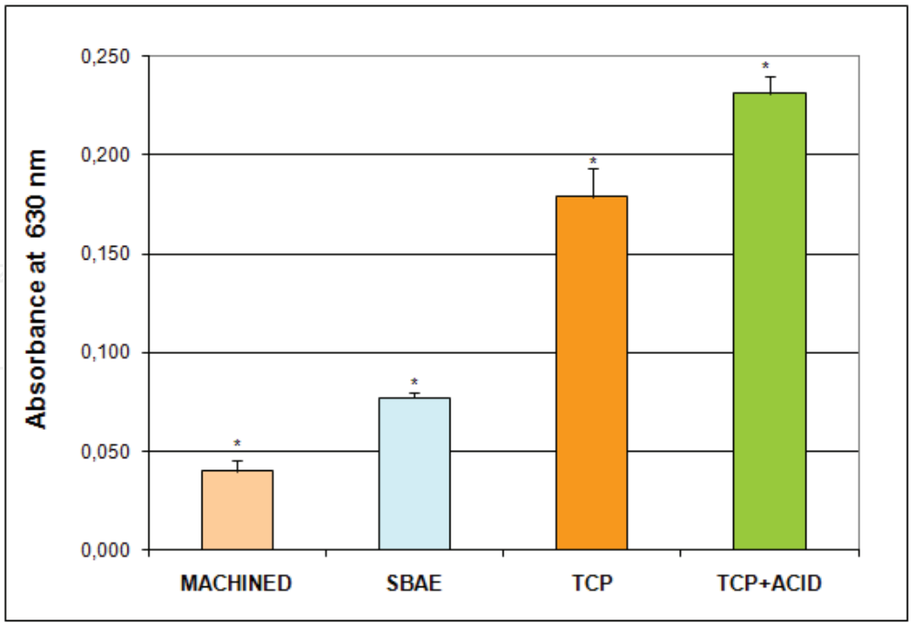

Fig. 6. Cell adhesion results after 24 hours of culture. Error bars = standard error. An asterisk indicates statistical difference between results at $p < 0.005$.

and 2, possibly caused by cell death during initial confluence. However, for machined, SBAE and TCP surfaces between day 2 and 5 proliferation levels increase almost linearly reaching a proliferation peak on day 6, after which the levels slightly decline until a final value on day 7. This proliferation peak at day 6 after culture was found to be higher on the SBAE surface. In contrast, proliferation on the TCP+acid surface shows a slow decrement between day 1 and day 2 together with an exponential-like increment that lasts until day 7. No statistical significant differences between results were found from days 1 to 7.

Concluding results for the adhesion assay showed that TCP and TCP+acid surfaces have better osteoinductive response than machined and SBA surfaces. Cell proliferation assay revealed that after 7 days of culture TCP+acid surface has the lowest proliferation rate, due to its increased surface roughness Aita et al. (2009); Bächle & Kohal (2004). The remarkable adhesion profile of the TCP surface and its considerable high proliferation rate after 7 days of culture were confirmed by the ALP activity results from which TCP surface has better performance and doubles the result obtained for the TCP+acid surface Vanegas et al. (2010). The results obtained suggest that TCP surface promote the formation of mineral deposits, i.e. osteoconduction, in a higher rate compared not only to the TCP+acid surface but also to the machined and SBA surfaces. None of the studied surfaces were toxic to the osteoblastic-like cells since all of them exhibited cell adhesion and proliferation profiles.

2.5 Mathematical modeling

Although at the bone-dental implant interface biological and mechanical factors converge, most of the mathematical models available only consider the mechanical factors obtaining conclusions regarding the long range viability of the implants, the loading distributions and the mechanical behavior of the materials used in the implant manufacture Geng & Tan (2001); Patra et al. (1998). In this type of models the formation of the bone-dental implant

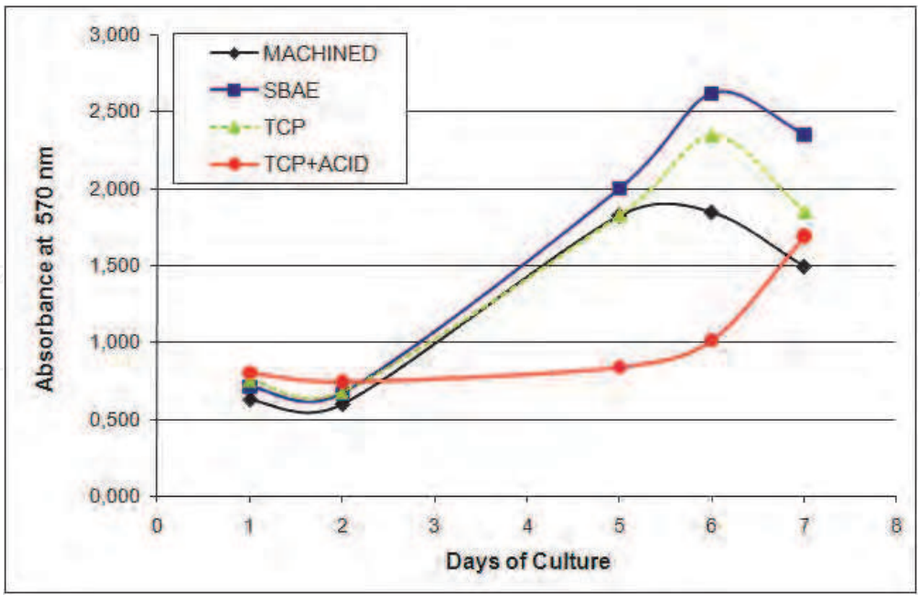

Fig. 7. Cell proliferation after 1, 2, 5, 6 and 7 days of culture.

interface is not considered and the assumed biological starting point is the complete and stable osseointegration Patra et al. (1998). There are also models approaching to the healing biological phenomena at the interface, describing fibrous tissue formation as the results of mechanical variables Huiskes et al. (1997) or by considering the phenomenological behavior of the mechanics involved Isaksson et al. (2008). Nevertheless, there are models with a biological framework that base their descriptions on phase changes at the interface Ambard & Swider (2006) and on variations of the cellular concentrations and extracellular matrix density Bailon-Plaza & van der Meulen (2001); Moreo et al. (2009). In this cases, the equations used include specific terms describing cellular processes as mitosis, proliferation, differentiation and apoptosis, as well as natural biological events leading to the formation, transformation and degradation of the extracellular matrix Bailon-Plaza & van der Meulen (2001); Geris et al. (2008); Moreo et al. (2009).

2.5.1 Mechanical approach

Mathematical modeling of a dental implant with a mechanical approach allows for the evaluation of different implant designs ensuring resistance to certain loading conditions Bonnet et al. (2009); Bülent (2002); Juodzbalys (2005); Kayabasi et al. (2006); Papavasiliou (1996); Poiate et al. (2008). The analysis of the bone-dental implant interface in these models is focused in the stress distribution around the host bone and the implant body, and in the effect of loading in the stability of the alveolar bone Geng & Tan (2001). It is then possible to redesign implants without the complications of physical manufacturing and experimentation saving money and time. Most of these models are computationally implemented through commercial available software that perform a numerical discretization using the finite differences method or the finite elements method Bonnet et al. (2009); Geng et al. (2001); Kayabasi et al. (2006); Poiate et al. (2008).

Most of the authors have reported simulations using geometrical bidimensional and tridimensional models obtaining a graphical sketch of the physical behavior of the interface

after loading. This same approach was used in a new numerical simulation of a bone-dental implant interface. Figure 8a shows the compact model of the interface where jaw bone and prosthesis are only visible. A more detail representation is shown in Figure 8b where prostheses were elevated to show three dental implants inserted in the jaw bone. Observe that the jaw bone was modeled as an external trabecular zone covering a cortical zone Davies (2003); Saffar et al. (1997). This model was implemented to performed a comparative study of the biomechanical behavior of individual prosthesis and ferulized prostheses used in oral rehab treatment at the posterior jawbone.

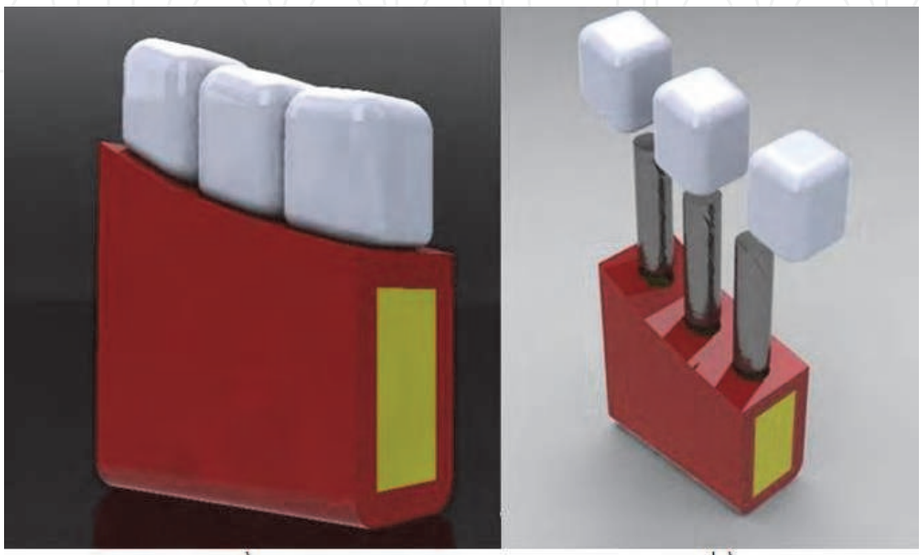

Fig. 8. Sketch of a geometrical model used to simulate a single-crown prosthesis dental-implant condition. a) Compact model. White: Prosthesis. Red: Trabecular bone. Yellow: Cortical bone. b) Detail of the model components. Gray: Dental implants.

We performed a loading conditions analysis at the interface. Shear and longitudinal loads exerted to the prosthesis during chewing induce axial forces and shear momentum resulting in stress gradients at the host bone and the implant body (Geng et al., 2001). Figure 9 shows a simulation of these loading environment on the geometrical mode of Figure 8. Loading conditions applied to the model are similar to those present in the oral cavity during chewing. We simplified these loads as static loads and stress distributions at the interface. Results show a color scale representing the magnitude of the von Misses stress. Maximum value obtained in this simulation was 62.87 MPa. If the yield stress of the dental implant is higher that this value, as is the case of titanium and stainless steel, good performance is expected. Furthermore, surrounding host bone shows an approximated stress value of 17 MPa, that should be compared with the range of functional stress that controls bone deposition and resorption (Geng & Tan, 2001; Rieger et al., 1990). Final conclusion obtained from the numerical results was that best performance is achieved when using single-crown prostheses.
Model simplifications are needed in the mechanical models to manage problems as considering the mechanical differences between cortical and trabecular bone, the complex implant geometries, boundary conditions, computational costs, among others. According to these, a good mechanical model may be formulated based on the following assumptions:

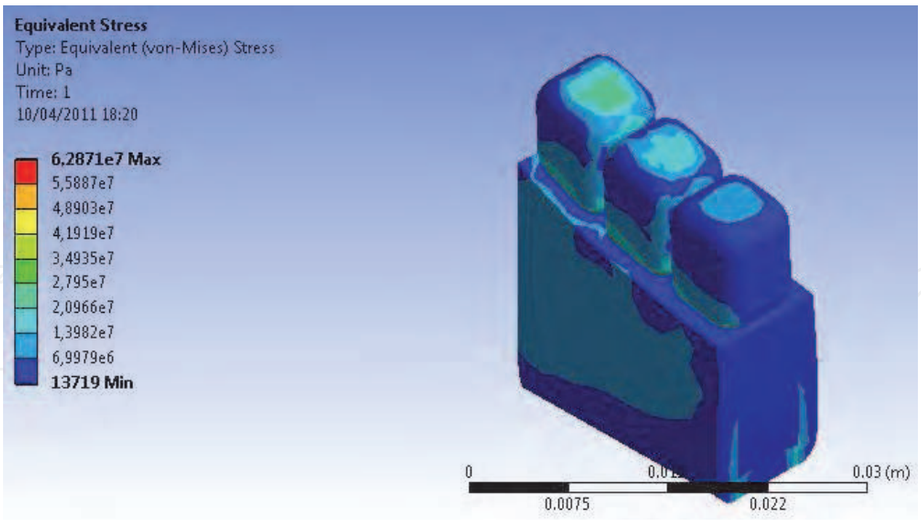

Fig. 9. Stress distribution for the model with single-crown prostheses.

1. For bidimensional studies, bone is modeled using simple rectangular configurations. For tridimensional models jaw is considered as an arch with rectangular sections (Geng et al., 2001). However, advanced medical imaging processing techniques may be useful to better model the geometry of the jaw bone, implants and prosthesis (Bonnet et al., 2009; Geng et al., 2001; Poiate et al., 2008).
2. Material properties for bone and dental implants are mostly considered as isotropic. However, is it well known that bone have orthotropic and anisotropic properties (Huiskes et al., 1997) since stress is not necessarily distributed in a uniform fashion rather than oriented in a preferential direction (Bonnet et al., 2009; Geng et al., 2001; Kayabasi et al., 2006). However, these material assumptions ensure its linearity and homogeneity and allow for an elastic behavior described by the Young and Poisson modules. Nevertheless, a more precise model should account for a better material description, including differences for trabecular and cortical bone, and for other surrounding tissues as muscles and epithelium (Geng et al., 2001).
3. Some assumptions for boundary conditions consider a fixed jaw. However, muscle and ligament function during chewing and functional movement of the temporomandibular joint should be modeled by using additional elements improving model realism and accuracy (Geng et al., 2001).
4. Most models regarding the bone-dental implant interface consider an initial complete osseointegration. However, we have shown that osseointegration is consequence of a biological process involving mechanical conditions. It has been found that osseointegration ratio depends on bone quality, stress distribution during wound healing, implant loading conditions and implant design, among others (Bonnet et al., 2009; Bülent, 2002; Geng et al., 2001; Juodzbalys, 2005; Kayabasi et al., 2006; Papavasiliou, 1996; Poiate et al., 2008). Therefore, a more realistic description of the interface should include additional considerations for the biological phenomena and its temporal evolution, if time evolution starting at implant placement wants to be addressed (Moreo et al., 2009).

2.5.2 Mechanobiological approach

A complete mechanobiological model for the formation of the bone-dental implant interface leading to the implant osseointegration is still not know, although several works have succeeded in the attempt of formulate a mathematical model including the biological and mechanical models related to some of the stages of tissue formation. This is the case of models for cell adhesion and proliferation (DiMilla et al., 1991; Moreo et al., 2008), models for coagulation (Colijn & Mackey, 2005; Vanegas et al., 2010), models for angiogenesis and cell contraction (Mantzaris et al., 2004; Tracqui et al., 2007), and models for bone formation (Amor et al., 2009; Moreo et al., 2009).

From the biological and mechanical reality of the healing and bone formation process at the bone-dental implant interface, and considering the results provided by the abovementioned mathematical models, the following elements should be considered in the formulation of a complete mechanobiological model for the bone-dental implant interface:

1. The biological stages of wound healing at the interface may be assumed as a sequence of events in a time scale divided in minutes, hours, days, weeks and months Ambard & Swider (2006); Aukhil (2000); Dimitriou et al. (2005).
2. The bleeding stage may be simplified as the formation of the fibrin clot by the reaction kinetics between thrombin and fibrinogen (Aukhil, 2000; Minors, 2007).
3. The fibrinolysis stage may be considered as a natural clot degradation term, whereas the fibroplasia and the angiogenesis can be simplified in a single event leading to synthesis of new collagen matrix (Häkkinen et al., 2000).
4. The formation and replacement of the collagen matrix by new bone is related to the presence of an specific concentration of osteogenic cells and the presence of a chemoatractant substance controlling cell migration and proliferation (Davies, 2003; Moreo et al., 2009; Puleo & Nanci, 1999).
5. The adequate bone formation around the dental implant depends on its surface topography and the formation of the cementation line (Davies, 2007; Kasemo, 2002).
6. The adhesion mechanical factors may be considered as part of the cell differentiation process and should be related to the implant surface topography and the implant osteoinduction and osteoconduction properties (Davies, 2007).
7. The contraction and activation mechanical factors are similar at a micro-structural level and therefore may be simplified as the viscoelastic behavior of the fibrillar fibrin matrix compounding the blood clot (Weisel, 2004) and guiding the bone forming process (Saffar et al., 1997; Stanford & Schneider, 2004).
8. The loading effects over the implant may be neglected if the recommended initial healing time of three to six months prior to prosthesis placement is considered (Branemark, 1983; Vanegas et al., 2009).
9. The surface irregularities of the dental implant influence the cell and proliferation profiles, as is shown through the experimental assays.
10. Numerical parameters needed for the mathematical formulation of the model may be obtained through experimental assays. Here, the mathematical formulation should provide enough justification for running the assays.

Most of these elements were used for the formulation of a new mathematical model with a mechanobiological approach (Vanegas et al., 2011). This model includes the biological stages described in Figure 3, some of the mechanical factors described in Figure 4, and the implant surface irregularities. A schematic of this new model is shown in Figure 10.

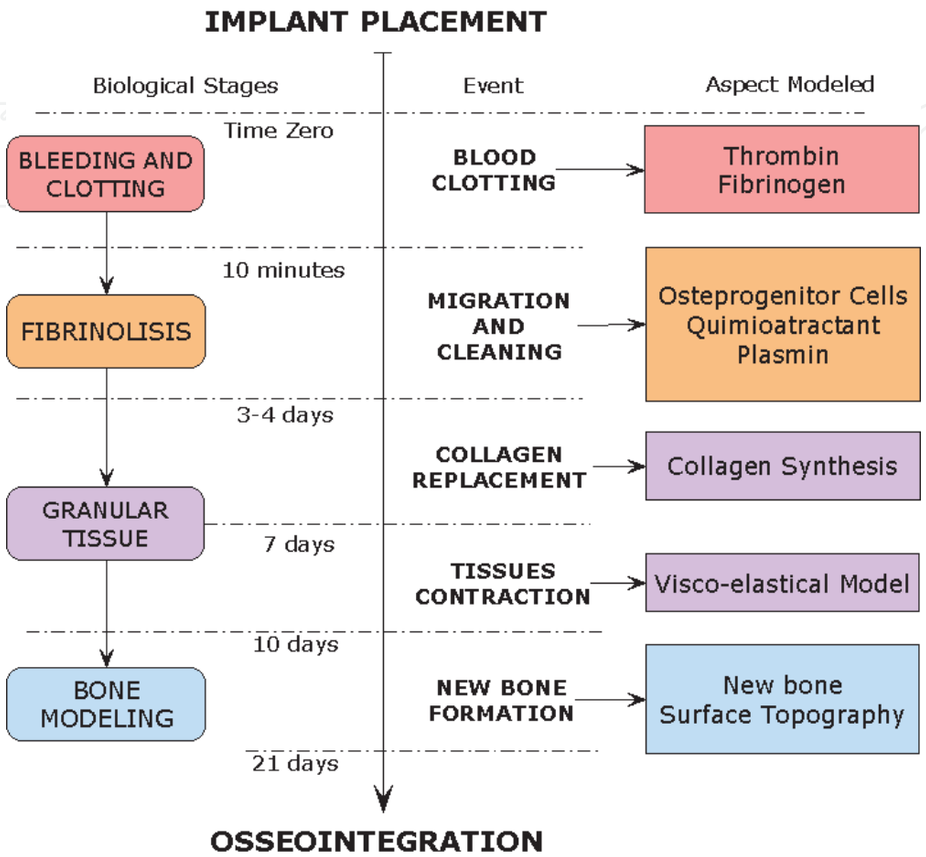

Fig. 10. Schematic of a mechanobiological model of the osseointegration of a dental implant. The sequence of biological stages is shown at the left side and the events and aspects modeled at each stage are shown at the right side. The boxes resume the most important elements used at each event that also represent the simplifications made to the complex chain of biological and mechanical phenomena leading to the dental implant osseointegration.

This model simplifies the biological wound healing process as a sequence of stages each one associated to a series of events. In this way, the bleeding and coagulation stage is simplified as the fibrin blood clot formation by the conversion reaction between thrombin and fibrinogen. During fibroplasia osteogenic cell migration is initiated by the presence of a chemoatractant substance at the same time that the fibrin clot is degraded by the plasmin activity. The new collagen matrix formation by the osteoprogenitor cells simplifies the fibroplasia and angiogenesis processes in a single stage called granular tissue (Aukhil, 2000). The displacement of the osteoprogenitor cells over the collagen matrix causes fibrillar contraction conditioned to the viscoelastic response of the fibers and the collagen mechanical properties. This contraction constitutes the interaction between biological and mechanical factors presented in this mechanobiological model. Finally, the new bone formation process,

conditioned to the surface topography of the implant included as a numerical parameter and the adequate formation of the cemented line due to the contact osteogenesis process, leads to the initial osseointegration of the dental implant.

3. Mini-implants

Anchorage is defined as resistance to unwanted tooth movement caused by the reacting force of orthodontic devices Proffit & Fields (1993). Anchorage control is essential in orthodontic biomechanics and is one of the prerequisites for successful orthodontic therapy Chaddad et al. (2008). Traditionally, orthodontic movement of a tooth is anchored by a large group of teeth so as to minimize undesired displacements. Adequate anchorage becomes difficult when teeth are missing or present pathologies like periodontal and endodontic diseases. Several methods have been introduced to provide additional anchorage in orthodontics. Intra-oral and extra-oral auxiliary devices can be used to assist movement, but the effectiveness of these measures depend on patient compliance Egolf et al. (1990).

Conventional dental implants have proven to be successful for orthodontic anchorage because they are suitable for loading and offer absolute anchorage Branemark (1983); Hansson et al. (1983). Since the application of earlier orthodontic forces affect implant osseointegration Adell et al. (1970); Gapski et al. (2003), osseous adaptation mechanisms taking place during orthodontic loading increase bone formation on localized zones in an attempt to counteract the loading effects Klein-Nulend et al. (2005); Wehrbein et al. (1999). However, the larger size of conventional endosseous implants limits their usage as anchorage devices leading to the development of specific orthodontic systems such as plates Chung et al. (2002), onplants Crismani et al. (2008), and mini-implants Kanomi (1997).

Mini-implants are titanium screws with smaller dimensions than dental implants (Figure 11). They are widely used in orthodontic treatments due to their few inherent limitations for the selection of the placement site, they have a simple surgical procedure for insertion and removal, have low cost, cause less trauma to the patient than dental implants and provide easy attachment for additional orthodontic devices Costa et al. (1998). The aim of the mini-implants is to remain stable at the oral cavity during the accomplishment of the orthodontic treatment. Once the treatment is finished, the mini-implant can be easily removed because their osseointegration ratio is only around 13% Zhao et al. (2009). This lower ratio suggest that the mini-implant primary stability is a consequence of a mechanical phenomenon of interaction with the surrounding cortical bone that avoids the need of an initial healing stage prior to orthodontic loading and also allows for an easy final removal Huja et al. (2005). Mini-implants insertion procedure starts with a vertical incision of 3 mm to 4 mm long. Incision borders are separated and a 0.09 mm diameter hole is drilled into the jaw bone. Placement site is cleaned using saline solution to avoid clinical complications. The mini-implant is then inserted leaving at least 2 mm of its distal side exposed in the oral cavity. Finally, orthodontic wire extensions are attached to the mini-implant head in order to include it in the orthodontic treatment Antoszewska et al. (2009).

Contrary to dental implants, mini-implants insertion angle is of paramount importance for the success of the orthodontic treatment Chaddad et al. (2008). It is recognized that a greater insertion angle is useful to increase the screw length inserted inside cortical bone causing an augmented fixation and higher primary stability Costa et al. (1998); Deguchi et al. (2006). Therefore, recommended insertion angles range between 15° and 90° depending of the maxilla dimensions Deguchi et al. (2006). After confirmation of primary stability by

Fig. 11. Different types of mini-implants.(A) Dual-top mini-implant ®(Jeil, Korea). (B) Link orthodontic implant ®(MIS, Israel)

evaluating absence of micromovements, immediate loading is performed with magnitudes ranging from 50 to 200 gr. Melsen & Costa (2002). These loads can be directly or indirectly applied using rubber bands or closed-helical springs after a responsible healing time of two weeks (Antoszewska et al., 2009; Zhao et al., 2009).
Once treatment has started, failure of the mini-implant may occur among other reasons because of low bone density and improper cortical bone thickness at the insertion site Motoyoshi, Inaba, Ono, Ueno & Shimizu (2009b). Experimental tests of these failure factors suggest that minimal cortical bone thickness should be 1 mm (Motoyoshi, Inaba, Ono, Ueno & Shimizu, 2009a). In addition, numerical analyses performed on mini-implant treatments have evaluated these same failure factors. Results from these analyses resume the mechanical conditions required for the use of mini-implants based on a predictive scheme supported on experimental evidence Motoyoshi, Okazaki & Shimizu (2009); Sung et al. (2010).

3.1 Experimental assays

In recent years, there has been an increased concern for better understanding the behavior of mini-implants as anchorage devices in the jaw bone. However, the suitable material, surface treatment, screw design, self-perforating screwing capability, ideal timing for loading and magnitude of loads are still not well defined Chaddad et al. (2008); Seong-Hun et al. (2008). Although the mini-implant stability should be preserved during the entire orthodontic treatment, this is something that not always can be assured since treatment times may vary and in some cases are longer than a year Antoszewska et al. (2009); Costa et al. (1998); Deguchi et al. (2006).
Immediate loading is one of the distinctive characteristics of mini-implants. Since bone healing at the interface is a dynamic process and external mechanical loading induces bone adaptation Klein-Nulend et al. (2005), keeping an unchanging long lasting interface after loading seems somehow unfeasible. Furthermore, it is not clear if the mini-implant may induce higher osseointegration ratios supporting immediate loading or if loads and micromovements induce fibrillar tissue formation at the bone-implant interface that hinder osseintegration Zhang et al. (2010). Recommended mini-implants are made of titanium due to

its biocompatibility and bioactivity Ellingsen et al. (2006); Ratner et al. (1996) but have smooth polished surfaces that may explained reduced osseointegration rates Davies (2007). However, a convenient osseointegration ratio may improve mini-implant stability during long lasting orthodontic treatments. Although evidence shows that mini-implants do not osseointegrate, there is no consensus on this matter and further experimental studies are needed to provide more details about the interface behavior Serra et al. (2008).

We have therefore performed a self-conducted experimental assays to analyze samples of bone surrounding mini-implants and evaluate the formation of the bone-implant interface. A total of fifteen 3-months-old male Wistar Rats SPF mean weight 350 gr. were housed with a 12-hour light/dark cycle and fed with a standard pellet diet and tap water at pleasure throughout the experiments Casale & Rivera (2010); Casale & Saavedra (2010). Principles of laboratory animal care and national laws were observed for the present study. Authorization for these experiments was issued by the Ethics Committee of the Dentistry Faculty of the Universidad Nacional de Colombia. Screw-shaped titanium (Ti_6Al_4Va) mini-implants of 10 mm length and 1.6 mm diameter (Link ®, MIS, Israel) were used in the assays. Sample screws were provided by MIS Implants Ltd. Immediate loading of 150 gr. was applied to all the mini-implants. A radiographic image of the insertion site is shown in Figure 12. Histological tissue behavior was evaluated 0, 8, 15, 45 and 120 days after insertion. A control group without immediate loading was also used.

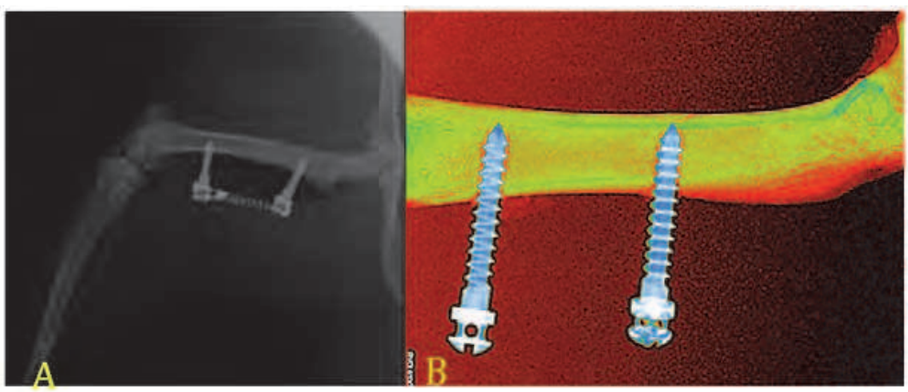

Fig. 12. A) SPF Wistar rat femur radiograph after mini-implant insertion and immediate loading using a nitinol spring (150gr). B) Digital radiograph after sacrifice.

Experimental data analyses (not shown) suggest that immediate loading does not affect the wound healing pattern. Histological observation of loaded samples showed that inflammation is activated between 0 and 15 days after insertion, bone activity under mechanical tension is started after 15 days of insertion and mature bone formation is started at day 45 after insertion. The histological activity in unloaded samples showed suitable bone healing barely starting on day 45 after insertion. These results suggest that wound healing and osseointegration at unloaded samples is similar to that exhibited on dental implants inserted in the cortical region.

Comparative additional experiments for orthodontic immediate loading of 150 gr and 350 gr. showed that higher loading is not feasible in mini-implants because mobility, displacement and screw instability are increased. Conversely, the application of this higher loading on mini-implants unloaded during the entire 45 days experimental time (late loading) showed no mobility or screw displacement. According to this, we provide histological evidence of

mini-implant osseointegration at the cortical region Casale & Rivera (2010); Casale & Saavedra (2010) (Figure 13).

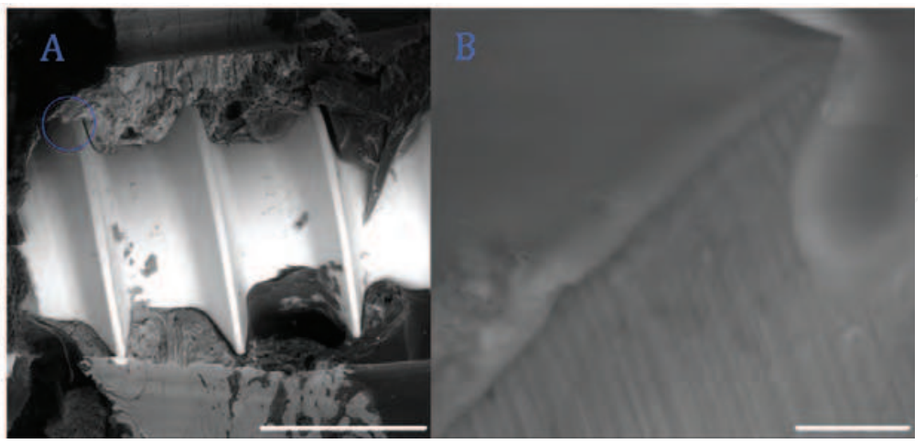

Fig. 13. A) SEM micrograph showing the bone-interface for a mini-implant without immediate loading. Scale bar = 1.0 mm. B) SEM micrograph for the encircled area of A) showing the same interface after 45 days with evidence of osseointegration with cortical bone. Scale bar = 2.0 μm

3.2 Mathematical modeling

Mathematical modeling regarding mini-implants, as applied to dental implants, allows for the description of the bone-implant interface, study factors leading to a successful insertion or a failure in the orthodontic treatment, and redesign mini-implants for better clinical performance. Available mathematical models have been used to study and predict mechanical events occurring during the orthodontic treatments Sung et al. (2010). These studies analyze the influence of mini-implants nearness to adjacent teeth roots, the effect of cortical bone height on treatment success and the consequences of inserting the mini-implant in surrounding poor quality bone Sung et al. (2010).

Since mini-implants are very similar to dental-implants, a good mathematical modeling approach for mini-implants may share conditions of those already mentioned for dental implants modeling. However, specific conditions should be addressed as follows:

1. Biological conditions in mini-implants treatments relate to the primary stability and osseointegration ratio. These same conditions should be accomplished in a good mathematical modeling of dental implants. Since the healing process is the same in dental implants and mini implants, a mathematical model of mini-implants may include the same biological stages as for dental implants. Nevertheless, an additional condition should state that the expected osseointegration ratio is around 13%. This allows for a relative simple adaptation of the models used in dental implants reducing the amount of bone formation around the implant surface, due basically to the absence of surface roughness Papadopoulos & Tarawneh (2007).
2. An additional biological condition for mini-implants successful treatment is the amount of cortical bone tissue in the insertion site. Related studies state that the minimal cortical bone thickness for an suitable functional stability of the device is 1 mm (Motoyoshi, Inaba, Ono, Ueno & Shimizu, 2009a). This condition may be addressed by controlling bone formation

process at the insertion site by an adequate loading stimulation or by increasing the area of the geometrical description (Figure 8).

3. In contrast to the biological approach of the model, the mechanical behavior is different of that regarding dental implants. Although the adhesion and contraction mechanical factors are still present and could be assumed the same as in dental implants, activations mechanical factors controlling the structural behavior of the bone-mini implant interface are quite different. Here, the direction and magnitude of loads, the mini-implant design and body geometry are different to those of dental implants. Therefore, models including these factors should be modified in order to address different types of treatments with specific loading orientations for increase anchorage, different insertions angles and different load transfer profiles.
4. Since mini-implants design have shorter dimensions that those found in dental implants, there must be a biological and mechanical relation of scaling with the surrounding tissues that should be analyzed in order to change the dimensions of the model to the shape profile of the used mini-implant.

4. Conclusions

Here we presented the principal characteristics of dental and mini-implants, the related bone healing process at the bone-implant interface and the mechanical factors involved. We also commented on self-conducted experimental approaches for evaluating the performance of these devices when in contact with living tissues. Finally, we presented a framework for the mathematical modeling of the bone-implant interface in both dental implant and mini-implant cases. Considering that mathematical models are approximations to the real osseointegration process at the bone-implant interface, there are some limitations inherent to the mathematical frameworks. These limitations are the simplification of the mechanobiological bone healing process, the initial conditions for the model, the adequate boundary conditions leading to the appropriate solution, and the model parameters, among many others. However, we should here highlight the prevalence of the latter in obtaining an accurate model.

Although in most of the cases some of the numerical parameter can be estimated from the available literature and others can be estimated from experimental results and previously reported numerical works, the exact value of many of them is an unknown and therefore adjustments are needed to obtain the expected solution. These adjustments may be performed by an iterative solution-based approach, a parameter sensitive analysis or a thorough mathematical analysis of the equations used Amor et al. (2009); Vanegas et al. (2011). Another approach is conducting specific experiments aimed at the quantification of detailed biological or mechanical quantities needed in the model formulation that are otherwise pointless and unjustified. This difficulty to obtain appropriate parameters from experimental evidence is a weakness shared in the models presented here with other works in the area of computational modeling of biological phenomena, and is a circumstance that should be considered before and during the process of model formulation.

Nevertheless these inherent limitations, results obtained from recent models Ambard & Swider (2006); Amor et al. (2009); Moreo et al. (2009); Vanegas et al. (2010; 2011) show that mathematical frameworks are suitable for being used as the methodological basis for the design of predictive tools aimed at the evaluation of the osseointegration ratio in dental and mini-implants considering patient characteristics, anatomy and jaw bone physiology, implant

design and surgical procedure used for inserting the implant Fragiskos & Alexandridis (2007); Gapski et al. (2003); Leckholm (2003); Stanford & Schneider (2004). Future applications may deal with developing additional models for the prediction of healing patterns in different types of tissue injury, different implant geometries and surfaces, and for the mechanobiological evaluation of other implantable devices.

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6. References

Adell, R., Hansson, B., Branemark, P. & Breine, U. (1970). Intra-osseous anchorage of dental prostheses ii. review of clinical approaches, *Scandinavian Journal of Plastic and Reconstructive Surgery* 4: 19–34.

Adell, R., Lekholm, U., Rockler, B. & Branemark, P. (1981). 15-year study of osseointegrated implants in the treatment of the edentulous jaw, *Journal of Oral Surgery* 10: 387–416.

Aita, H., Hori, N., Takeuchi, M., Suzuki, T., Yamada, M., Anpo, M. & Ogawa, T. (2009). The effect of ultraviolet functionalization of titanium on integration with bone, *Biomaterials* 30: 1015–1025.

Albrektsson, T. & Johansson, C. (2001). Osteoinduction, osteoconduction and osseointegration, *European Spine Journal* 10: S96–S101.

Ambard, D. & Swider, P. (2006). A predictive mechano-biological model of the bone-implant healing, *European Journal of Mechanics and Solids* 25: 927–937.

Amor, N., Geris, L., Vander-Sloten, J. & Van-Oosterwyck, H. (2009). Modelling the early phases of bone regeneration around an endosseous oral implant, *Computer Methods in Biomechanics and Biomedical Engineering* 12(4): 459–468.

Anselme, K. (2000). Osteoblast adhesion on biomaterials, *Biomaterials* 21: 667–681.

Antoszewska, J., Papadopoulos, M., Park, H. & Ludwigd, B. (2009). Five-year experience with orthodontic miniscrew implants: A retrospective investigation of factors influencing success rates, *American Journal of Orthodontics and Dentofacial Orthopedics* 136: 158.e1–158.e10.

Aparicio, C. (2005). *Tratamientos de superficie sobre titanio comercialmente puro para la mejora de la osteointegración de los implantes dentales*, PhD thesis, Universitat Politécnica de Catalunya. Barcelona, España.

Arzate, H., Alvarez-Pérez, M., Aguilar-Mendoza, M. & Alvarez-Fregoso, O. (1998). Human cementum tumor-derived cells have different features from human osteoblastic cells in-vitro, *Journal of Periodontal Research* 33: 249–258.

Arzate, H., Alvarez-Pérez, M., Alvarez-Fregoso, O., Wusterhaus-Chávez, A., Reyes-Gasga, J. & Ximénez-Fyvie, L. (2002). Electron microscopy, micro-analysis and x-ray diffraction characterizationof the mineral-like tissue deposited by human cementum tumor-derived cells, *Journal of Dental Research* 79: 28–34.

Aukhil, I. (2000). Biology of wound healing, *Periodontology 2000* 22: 44–50.

Bächle, M. & Kohal, R. (2004). A systematic review of the influence of different titanium surfaces on proliferation, differentiation and protein synthesis of osteoblast-like mg63 cells, *Clinical Oral Implants Research* 15(6): 683–92.

Bailon-Plaza, A. & van der Meulen, M. (2001). A mathematical framework to study the effects of growth factor influences on fracture healing, *Journal of Theoretical Biology* 212: 191–209.

Bonnet, A., Postaire, M. & Lipinski, P. (2009). Biomechanical study of mandible bone supporting a four-implant retained bridge finite element analysis of the influence of bone anisotropy and foodstuff position, *Elsevier* 31: 806–815.

Branemark, P. (1983). Osseointegration and its experimental background, *Journal of Prosthetic Dentistry* 50(3): 399–410.

Branemark, P., Breine, U., Adell, R., Hansson, O., Lindstöm, J. & Ohlsson, A. (1969). Intra-osseous anchorage of dental prostheses i. experimental studies, *Scandinavian Journal of Plastic and Reconstructive Surgery* 3: 81–100.

Bülent, E. (2002). Numerical analysis of a dental implant system in three Ű dimension, *Advances in engineering software* 33: 109–113.

Burger, E., Klein-Nulend, J. & Mullender, M. (2005). Mechanobiology of bone, *in* H. Petite & R. Quarto (eds), *Engineered Bone*, Landes Bioscience-Eurekah.com, pp. 28–44.

Casale, M. & Rivera, P. (2010). *Evaluacion biomecanica e histologica de implantes ortodonticos de titanio cargados con diferentes brazos de palanca*, Master's thesis, Universidad Nacional de Colombia, Posgrado de Ortodoncia, Facultad de Odontologia.

Casale, M. & Saavedra, M. (2010). *Evaluacion del comportamiento tisular y biomecanico a la carga inmediata y tardia de implantes ortodonticos de titanio*, Master's thesis, Universidad Nacional de Colombia, Posgrado de Ortodoncia, Facultad de Odontologia.

Chaddad, K., Ferreira, A., Geurs, N. & Reddy, M. (2008). Influence of surface characteristics on survival rates of mini-implants, *Angle Orthodontist* 78: 107–113.

Chung, K., Kim, Y., Linton, J. & Lee, Y. (2002). The miniplate with tuve for skeletal anchorage, *Journal of Clinical Orthodontics* 36: 407–412.

Colijn, C. & Mackey, M. (2005). A mathematical model of hematopoiesis i. periodic chronic myelogenous leukaemia, *Journal of Theoretical Biology* 237: 117–132.

Collen, D. & Lijnen, H. (1991). Basic and clinical aspects of fibrinolysis and thrombolysis, *Blood* 78: 3114–3124.

Costa, A., Raffaini, M. & Melsen, B. (1998). Miniscrews as orthodontic anchorage: a preliminary report, *International journal of adult orthodontic and orthognathic surgery* 13: 201–209.

Crismani, A., Bernhart, T., Tangl, S., Celar, A., Fugger, G., Gruber, R., Bantleon, H. & Watzek, G. (2008). Osseointegration and subperiosteal anchoring device in minipig mandible, *American journal of orthodontics and dentofacial orthopedics* 133: 743–747.

Davies, J. (2003). Understanding peri-implant endosseous healing, *Journal of Dental Education* 67(8): 932–949.

Davies, J. (2007). Bone bonding at natural and biomaterial surfaces, *Biomaterials* 28: 5058–5067.

Deguchi, T., Nasu, M., Murakami, K., Yabuuchi, T., Kamioka, H. & Yamamoto, T. (2006). Quantitative evaluation of cortical bone thickness with computed tomography scanning for orthodontic implants, *American Journal of Orthodontics and Dentofacial Orthopedics* 126(6): 721.e7–721.e12.

DiMilla, P., Barbee, K. & Luffenburger, D. (1991). Mathematical model for the effects of adhesion and mechanics on cell migration speed, *Biophysics Journal* 60: 15–37.

Dimitriou, R., Tsiridis, E. & Giannoudis, P. (2005). Current concepts of molecular aspects of bone healing, *Injury: International Journal of the Care of the Injured* 36: 1392–1404.

Egolf, R., BeGole, E. & Upshaw, H. (1990). Factors associated with orthodontic patient compliance with intra-oral elastic and headgear wear, *American Journal of Orthodontics and Dentofacial Orthopedics* 97: 336–348.

Ellingsen, J., Thomsen, P. & Lyngstadaas, P. (2006). Advances in dental implant materials and tissue regeneration, *Periodontology 2000* 41: 136–156.

Fragiskos, F. & Alexandridis, C. (2007). Osseointegrated implants, *in* F. Fragiskos & C. Alexandridis (eds), *Oral Surgery*, Springer Berlin Heidelberg, pp. 337–348.

Furie, B. & Furie, B. (2005). Thrombus formation in vivo, *Journal of Clinical Investigation* 115: 3355–3362.

Gapski, R., Wang, H., Mascarenhas, P. & Lang, N. (2003). Critical review of immediate implant loading, *Clinical Oral Implants Research* 14: 515–527.

Geng, J., Tan, K. & Liu, G. (2001). Application of finite element analysis in implant dentistry: a review of literature, *Journal prosthet dental* 85: 585–598.

Geng, J. & Tan, KBC and, L. G. (2001). Application of finite element analysis in implant dentistry: A review of literature, *Journal of Prosthetic Dentistry* 85: 585–598.

Geris, L., Gerisch, A., Vander-Sloten, J., Weiner, R. & Van-Oosterwyck, H. (2008). Angiogenesis in bone fracture healing: A bioregulatory model, *Journal of Theoretical Biology* 251: 137–158.

Gorkun, O., Veklich, Y., Weisel, J. & Lord, S. (1997). The conversion of fibrinogen to fibrin: Recombinant fibrinogen typifies plasma fibrinogen, *Blood* 89(12): 4407–4414.

Gracco, A., Cirignaco, A., Cozzani, M., Boccaccio, A., Pappalettere, C. & Vitale, G. (2009). Numerical/experimental analysis of the stress field around miniscrews for orthodontic anchorage, *European Journal of Orthodontics* 31: 12–20.

Häkkinen, L., Uitto, V. & Larjava, H. (2000). Cell biology of gingival wound healing, *Periodontology 2000* 24: 127–152.

Hansson, H., Albrektsson, T. & Branemark, P. (1983). Structural aspects of the interface between tissue and titanium implants, *Journal of Prosthetic Dentistry* 50(1): 108–113.

Hayman, E., Engvall, E., A'Hearn, E., Barnes, D., Pierschbacher, M. & Ruoslahti, E. (1982). Cell attachment on replicas of sds polyacrylamide gels reveals two adhesive plasma proteins, *Journal of Cell Biology* 95: 20–23.

Heydenrijk, K., Raghoebar, G., Meijer, H., van der Reijden, W., van Winkelhoff, A. & Stegenga, B. (2002). Two-stage imz implants and iti implants inserted in a single-stage procedure. a prospective comparative study, *Clinical Oral Implants Research* 13: 371–380.

Huang, Y., Xiropaidis, A., Sorensen, R., Albandar, J., Hall, J. & Wikesjö, U. (2005). Bone formation at titanium porous oxide [tiunite] oral implants in type iv bone, *Clinical Oral Implants Research* 16: 105–111.

Huiskes, R., van Driel, W., Prendergast, P. & Soballe, K. (1997). A biomechanical regulatory model for periprosthetic fibrous-tissue differentiation, *Journal of Materials Science: Materials in Medicine* 8: 785–788.

Huja, J., Litsky, A., Beck, F., Johnson, K. & Larsen, P. (2005). Pull-out strength of monocortical screws placed in the maxillae and mandibles of dogs, *American journal of orthodontics and dentofacial orthopedics* 127: 307–313.

Isaksson, H., van Donkelaar, C., Huiskes, R. & Ito, K. (2008). A mechano-regulatory bone-healing model incorporating cell-phenotype specific activity, *Journal of Theoretical Biology* 252: 230–246.

Juodzbalys, G. (2005). Stress distribution in bone: Single Ű unit implant prostheses vennered with porcelain or a new composite material, *Implant Dental* 14: 166–175.

Kanomi, R. (1997). Mini-implants for orthodontic anchorage, *Journal of clinical orthodontics* 36: 763–767.

Kasemo, B. (2002). Biological surface science, *Surface Science* 500: 656–677.

Kayabasi, O., Yüzbasioglu, E. & Erzincanli, F. (2006). Static, dynamic and fatigue behaviors of dental implant using finite element method, *Advances in engineering software* 37: 649–658.

Klein-Nulend, J., Bacabac, R. & Mullender, M. (2005). Mechanobiology of bone tissue, *Pathologie Biologie* 53: 576–580.

Knothe-Tate, M. (2003). Whither flows the fluid in bone? an osteocyte's perspective, *Journal of Biomechanics* 36: 1409–1424.

Lang, N., Araujo, M. & Karring, T. (2003). Alveolar bone formation, *in* J. Lindhe, T. Karring & N. Lang (eds), *Clinical Periodontology and Implant Dentistry*, Blackwell Munksgaard, pp. 866–896.

Leckholm, U. (2003). The surgical site, *in* J. Lindhe, T. Karring & N. Lang (eds), *Clinical Periodontology and Implant Dentistry*, Blackwell Munksgaard, pp. 852–865.

Li, W., Chong, S., Huang, E. & Tuan, T. (2003). Plasminogen activator/plasmin system: A major player in wound healing?, *Wound Repair and Regeneration* 11: 239–247.

Lindhe, J., Karring, T. & Araujo, M. (2003). Anatomy of the periodontium, *in* J. Lindhe, T. Karring & N. Lang (eds), *Clinical Periodontology and Implant Dentistry*, Blackwell Munksgaard, pp. 3–49.

Mann, K. (2003). Thrombin formation, *Chest* 124: 4–10.

Mantzaris, N., Webb, S. & Othmer, H. (2004). Mathematical modeling of tumor-induced angiogenesis, *Journal of Mathematical Biology* 49: 111–187.

Martínez, J., Sánchez, C., Trapero, C., Martínez, M. & García, F. (2002). Diseño de los implantes dentales: estado actual, *Avances en Periodoncia* 14(3): 129–136.

Matsuno, H., Yokoyama, A., Watari, F., Uo, M. & Kawasaki, T. (2001). Biocompatibility and osteogenesis of refractory metal implants, titanium,hafnium, niobium, tantalum and rhenium, *Biomaterials* 22: 1253–1262.

Melsen, B. & Costa, A. (2002). Immediate loading of implants used for orthodontic anchorage, *Clinical orthodontics and research* 3: 23–28.

Metikos-Hukovic, M., Kwokal, A. & Piljac, J. (2003). The influence of niobium and vanadium on passivity of titanium-based implants in physiological solution, *Biomaterials* 24: 3765–3775.

Meyer, U. & Wiesmann, H. (2006). *Bone and Cartilage Engineering*, Springer-Verlag, Berlin Heidelberg.

Minors, D. (2007). Haemostasis, blood platelets and coagulation, *Anaesthesia and intensive care medicine* 8(5): 214–216.

Moreo, P., García-Aznar, J. & Doblaré, M. (2008). Modeling mechanosensing and its effect on the migration and proliferation of adherent cells, *Acta Biomaterialia* 4: 613–621.

Moreo, P., García-Aznar, J. & Doblaré, M. (2009). Bone ingrowth on the surface of endosseous implants. part i: Mathematical model, *Journal of Theoretical Biology* 260: 1–12.

Mosmann, T. (1983). Rapid colorimetric assay for cellular growth and survival: Application to proliferation and cytotoxicity assays, *Journal of Immunological Methods* 65: 55–63.

Motoyoshi, M., Inaba, M., Ono, A., Ueno, S. & Shimizu, N. (2009a). The effect of cortical bone thickness on the stability of orthodontic mini-implants and on the stress distribution in surrounding bone, *International journal of oral and maxillofacial surgery* 38: 13–18.

Motoyoshi, M., Inaba, M., Ono, A., Ueno, S. & Shimizu, N. (2009b). The effect of cortical bone thickness on the stability of orthodontic mini-implants and on the stress distribution in surrounding bone, *International journal of oral and maxillofacial surgery* 38(1): 13–18.

Motoyoshi, M Ueno, S., Okazaki, K. & Shimizu, N. (2009). Bone stress for a mini-implant close to the roots of adjacent teeth - 3d finite element analysis, *International journal of oral and maxillofacial surgery* 38: 363–368.

Niinomi, N. (2003). Recent research and development in titanium alloys for biomedical applications and healthcare goods, *Science and Technology of Advanced Materials* 4: 445–454.

Papadopoulos, M. & Tarawneh, F. (2007). The use of miniscrew implants for temporary skeletal anchorage in orthodontics: A comprehensive review, *Oral surgery, oral medicine, oral pathology, oral radiology & endodontics* 103: e6–e15.

Papavasiliou, G. (1996). Three Ű dimensional finite element analysis of stress distribution around single tooth implants as a function of bony support, prosthesis type, and loading during function, *Journal prosthet dental* 76: 633–640.

Pasi, K. (1999). Hemostasis, *in* D. Perry & K. Pasi (eds), *Hemostasis and Thrombosis Protocols*, Humana Press, pp. 3–24.

Patra, A., DePaolo, J., D'Souza, K., Detalla, D. & Meenaghan, M. (1998). Guidelines for analysis and redesign of dental implants, *Implant Dentistry* 7(4): 355–366.

Poiate, I., Vasconcellos, A., Andueza, A., Pola, I. & Poiate, E. (2008). Three dimensional finite element analyses of oral structures by computerized tomography, *Journal of bioscience and bioengineering* 106(6): 606–609.

Proffit, W. & Fields, H. (1993). *Mechanical principles in orthodontic force control. In: Contemporary Orthodontics*, Mosby.

Puleo, D. & Nanci, A. (1999). Understanding and controlling the bone-implant interface, *Biomaterials* 20: 2311–2321.

Ratner, B., Hoffman, A., Shoen, F. & Lemons, J. (1996). *Biomaterials Science: An Introduction to Materials in Science*, Academic Press, San Diego.

Rieger, M., Adams, M. & Kinzel, G. (1990). Finite element analysis of eleven endosseus implants, *Journal of Prosthetic Dentistry* 63(4): 457–465.

Rodil, S., Olivares, R. & Arzate, H. (2004). In vitro cytotoxicity of amorphous carbon films, *Biomedical Materials and Engineering* 15: 101–112.

Rodil, S., Olivares, R., Arzate, H. & Muhl, S. (2003). Properties of carbon films and their biocompatibility using in-vitro tests, *Diamond and Related Materials* 12: 931–937.

Saffar, J., Lasfargues, J. & Cherruau, M. (1997). Alveolar bone and the alveolar process: The socket that is never stable, *Periodontology 2000* 13: 76–90.

Seong-Hun, K., Jae-Hee, C., Kyu-Rhim, C. & Yoon-A, K. (2008). Removal torques values of surface-treated mini-implants after loading, *American journal of orthodontics & dentofacial orthopedics* 134(1): 35–43.

Serra, G., Morais, L., Elias, C., Meyers, M., Andrade, L. & Muller, M. (2008). Sequential bone healing of immediately loaded mini-implants, *American journal of orthodontics & dentofacial orthopedics* 134(1): 44–42.

Sikavitsas, V., Temenoff, J. & Mikos, A. (2001). Biomaterials and bone mechanotransduction, *Biomaterials* 22: 2581–2593.

Stanford, C. & Schneider, G. (2004). Functional behavior of bone around dental implants, *Gerodontology* 21: 71–77.

Sung, S., Jang, G., Chun, Y. & Moond, Y. (2010). Effective en-masse retraction design with orthodontic mini-implant anchorage: A finite element analysis, *American Journal of Orthodontics and Dentofacial Orthopedics* 137: 648–657.

Tracqui, P., Namy, P. & Ohayon, J. (2007). In vitro tubulogenesis of endothelial cells: Analysis of a bifurcation process controlled by a mechanical switch, *in* A. Deutsch, L. Brusch, H. Byme, G. de Vries & H. Herzel (eds), *Mathematical Modeling of Biological Systems*, Vol. I, Springer- Birkhäuser, pp. 47–57.

Van der Meulen, M. & Huiskes, R. (2002). Why mechanobiology? a survey article, *Journal of Biomechanics* 35: 401–414.

Vanegas, J., Landinez, N. & Garzón-Alvarado, D. (2010). Mathematical model of the coagulation at the bone-dental implant interface, *Computers in Biology and Medicine* 40(10): 791–801.

Vanegas, J., Landinez, N., Garzón-Alvarado, D. & Casale, M. (2011). A finite element method approach for the mechanobiological modeling of the osseointegration of a dental implant, *Computer Methods and Programs in Biomedicine* 101: 297–314.

Vanegas, J., Landínez, N. & Garzón, D. (2009). Generalidades de la interfase hueso-implante dental, *Revista Cubana de Investigaciones Biomédicas* 28(3): 130–146.

Vanegas, J., Garzón, D. & Casale, R. (2010). Interacción entre osteoblastos y superficies de titanio: aplicación en implantes dentales, *Revista Cubana de Investigaciones Biomédicas* 29(1): 51–68.

Watari, F., Yokoyama, A., Omori, A., Hirai, T., Kondo, H., Uo, M. & Kawasaki, T. (2004). Biocompatibility of materials and development to functionally graded implantf or biomedical application, *Composites Science and Technology* 64: 893–908.

Wehrbein, H., Yildirim, M. & Diedrith, P. (1999). Osteodynamics around orthodontically loaded short maxillary implantes, *Jorunal of Orofacial Orthopedics* 60: 409–415.

Weisel, J. (2004). The mechanical properties of fibrin for basic scientists and clinicians, *Biophysical Chemistry* 112: 267–276.

Wennerberg, A., Albrektsson, T. & Lindhe, J. (2003). Surface topography of titanium dental implants, *in* J. Lindhe, T. Karring & N. Lang (eds), *Clinical Periodontology and Implant Dentistry*, Blackwell Munksgaard, pp. 821–828.

Zhang, L., Zhao, Z. & Li, Y. (2010). Osseointegration of orthodontic micro-screw after immediate and early loading, *Angle orthdontists* 80(2): 354–360.

Zhao, L., Xu, Z., Yang, Z., Wei, X., Tang, T. & Zhao, Z. (2009). Orthodontic mini-implant stability in different healing times before loading: A microscopic computerized tomographic and biomechanical analysis, *Oral surgery, oral medicine, oral pathology, oral radiology & endodontics* 108: 196–202.

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These contribution books collect reviews and original articles from eminent experts working in the interdisciplinary arena of biomaterial development and use. From their direct and recent experience, the readers can achieve a wide vision on the new and ongoing potentials of different synthetic and engineered biomaterials. Contributions were not selected based on a direct market or clinical interest, than on results coming from very fundamental studies which have been mainly gathered for this book. This fact will also allow to gain a more general view of what and how the various biomaterials can do and work for, along with the methodologies necessary to design, develop and characterize them, without the restrictions necessarily imposed by industrial or profit concerns. The book collects 22 chapters related to recent researches on new materials, particularly dealing with their potential and different applications in biomedicine and clinics: from tissue engineering to polymeric scaffolds, from bone mimetic products to prostheses, up to strategies to manage their interaction with living cells.

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