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Evaluation of Soft and Hard Tissue Remodelling in Post-Extraction Immediate Dental Implants Placed with a Flap and Flapless Approach in the Aesthetic Region. Clinical and Radiographic Prospective Evaluation at One Year

Valoración del Remodelado del Tejido Óseo y Gingival en Implantes Insertados en Alveolos Post-Exodoncia con y sin Colgajo Mucoperióstico en Zona Estética. Estudio Clínico y Radiológico Prospectivo a 1 Año

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Evaluation of soft and hard tissue remodelling in post-extraction immediate dental implants placed with a flap and flapless approach in the aesthetic region. Clinical and radiographic prospective evaluation at one year.

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SUMMARY.

Aim: The aim of this PhD investigation is to compare the survival/success rate, aesthetic outcomes and buccal plate resorption of immediate dental implants (Biomimetic OCEAN, Avinent®) using a flap vs. flapless approach. This was assessed with clinical/ radiographic information, aesthetic indexes and patient's reported outcomes at one-year post-loading.

Materials and methods: Subjects requiring single tooth extraction in the anterior and premolar areas were recruited for this study. Implant position and choice of platform were restoratively driven and aiming to optimise aesthetics. In the control group, implant placement was performed with the elevation of a mucoperiosteal flap whereas in the test group this was performed flapless. Measurements and analyses were performed by masked examiners.

Results: 40 cases were selected and randomised, of which 28 were included for the elaboration of this PhD. No implants were lost during the duration of this study. Success rate varied from 62.9%-84.6% in the test group and 84.6% to 92.3% in the control group. No statistically significant differences were noted in buccal plate resorption/remodelling between control (0.72 +/-0.22) and test group (0.92+/-0.31), PES (10.54 control vs. 10.80 test), WES (6.97 control vs. 6.95 test) or patient's reported outcomes at one-year post-loading. Mixed effect model for Total PES and WES score were created using treatment group (flap/flapless), dentist groups, and buccal plate thickness at 12 months as fixed effects covariates while measurement occasion nested examiner as random effects covariate. The only statistically significant association was found between "PES" and "Periodontist/orthodontist group".

Conclusions: Immediate dental implant treatment with a flap/flapless approach seemed to provide a similar survival rate, mean buccal plate resorption/remodelling, mean PES/WES scores and patients' satisfaction. However, a flapless approach resulted in lower success rates vs. a flap approach although this was not statistically significant. Optimal aesthetics seemed difficult to achieve and failures were quite prevalent in both groups despite of careful selection and patients been treated by an experienced clinician. More prospective, randomised and better powered studies are needed to monitor soft/hard tissue dynamics over longer time periods of time as it is currently unclear to what extent a flap vs. flapless approach may influence the aesthetic outcomes in the long term. For this, the wider use of accepted aesthetic indexes, validated PROMs tools and CBCT examination in futures studies would be needed to objectively monitor these outcomes over the time.

KEYWORDS:
Dental Implant, Immediate Placement, Flapless, Pink Aesthetic Score, Patient's Reported Outcomes, Vestibular Cortical Plate.

ABBREVIATIONS:

ACTG: Autogenous connective tissue graft.
ADM: Acellular dental matrix.
BMPs: Bone morphogenetic proteins.
Bop: Bleeding on probing.
B-TCP: Beta tricalcium phosphate.
CAL: Clinical attachment level.
CaP: Calcium Phosphate.
CBCT: Cone beam computed tomography.
DBBM: Deproteinised bovine bone mineral.
DFDBA: Demineralized freeze-dried bone allograft.
DI: Dental implant.
ePTFE: Expanded polytetrafluoroethylene.
FGF: Fibroblast growth factor.
FMBS: Full-mouth bleeding score.
FMPS: Full-mouth plaque score.
FPD: Fix dental prosthesis.
GBR: Guided bone regeneration.
GDP: General Dental practitioner.
GTR: Guided tissue regeneration.
HBO: Hyperbaric oxygen.
IC: Intercuspal.
IGF1: Insulin-like growth factor 1.
OI: Osseointegration.
OR: Odds ratio.
ORN: Osteoradionecrosis.
PDGF: Platelet-derived growth factor.
PDL: Periodontal ligament.
PES: Pink aesthetic score.
PPD: Probing pocket depth.
PRF: Platelet-rich fibrin.
PROMs: Patient reported outcome measures.
REC: Recession
RPD: Removable dental prosthesis.
TGFbeta: Transforming growth factor beta.
VAS: Visual analogue scale.
WES: White aesthetic score.

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I. INTRODUCTION AND THEORETICAL FRAMEWORK

1.1 HISTORY OF DENTAL IMPLANTS.

The introduction of dental implants (DI) as an option to replace missing teeth is considered one of the most revolutionary developments in modern dentistry. Up to that point, the main treatment modalities to replace the missing dentition presented some drawbacks that made them not suitable for every patient, being removable dental prosthesis (RPD) and fixed dental prosthesis (FPD) the main ones. RPD had the main inconvenience that it was a removable solution, it required adaptation of the musculature of the oral cavity (Dragobetskii, 1992), it often affected the gustatory perception (when hard palate was covered) and in cases where the alveolar ridge was extremely resorbed, removable prosthesis was far from being an ideal solution due to its mobility and decreased masticatory ability (Breustedt, 1978). On the other hand, FPD were traditionally regarded as a better option (when feasible) to replace teeth as it was a cemented prosthesis that the patient often felt as part of his/her dentition in contrast to RPD that required an adaptive period and it had to be removed on a regular basis (for cleaning purposes mainly). However, the need to perform preparation of the teeth serving as abutments had undesirable side effects that would frequently jeopardize the long-term success of this treatment modality. Evidence reports that teeth prepared as potential abutments are likely to experience pulp damage (Eriksson & Albrektsson, 1983), are prone to secondary caries and their long-term success rate is lower compared to dental implants (Pjetursson, Bragger, Lang and Zwahlen, 2007). Some of these undesirable effects have been greatly reduced by the introduction and improvement of newer adhesive-based techniques that do not require such as an aggressive preparation of the abutment teeth. However still they do not seem to be as successful as DI in the long term (Pjetursson et al., 2007).

DI were first introduced by Ingvar Branemark in early 1960. Through a series of studies, it was concluded that DI made of titanium could successfully osseointegrate in the host's bone (Branemark et al., 1977). This process of osseointegration (OI) was defined later by Albrektsson as "*a direct functional and structural connection between living bone and the surface of a load carrying DI*" (Albrektsson, Brånemark, Hansson & Jj, 1981). Another definition was provided by Schroeder and the term "*functional ankylosis*" was used to describe the rigid fixation of the implant to the jaw bone and stated that *"new bone is laid down directly upon the DI surface, provided that the rules for atraumatic implant placement are followed and the DI exhibits primary stability*" (Schroeder, Pohler & Sutter (1976); Schroeder, van der Zypen, Stich & Sutter (1981)). This process has been extensively studied due to the importance of the understanding wound healing in the design of new approaches to optimise healing times as well as finding new materials/implant surfaces to favour it.

1.2 BIOLOGIC PRINCIPLE OF OSSEOINTEGRATION.

The initial protocol described by Branemark was designed to replace teeth in completely edentulous arches, the healing periods were relatively long (six months) before these DI could be restored (Adell, Lekholm, Rockler & Brånemark, 1981) and the DI surface was what we call today a “machined surface” of minimal roughness. As a result of the evolution in this field, new applications of dental implants have been developed, such as replacement of single-unit teeth, and healing periods have been shortened as a consequence of a better understanding of the healing mechanism, optimised surgical techniques and improvements of DI surfaces.

At cellular level, the bone is a mineralised tissue that is formed from an array of cell types and an organic matrix that is strengthened by matrix-associated calcium minerals, primarily calcium and phosphate in the form of hydroxyapatite. Cells, matrix and minerals are connected in a special way to give bone its unique biophysical and biological properties (Landis, 1999). There are two types of bone with differentiated structural and functional features, the cortical and the trabecular bone. The structure of the cortical and the trabecular system is optimised to transfer the loads through the bone by a dynamic feedback between load perception of cells and their subsequent cellular reaction. The differences in the histological and ultrastructural appearance of the two tissue types are related to some extent to their functions. The cortical bone provides mechanical and protective functions whereas cancellous bone is mainly involved in metabolic functions (e.g. calcium homeostasis). The different proportions in these types of bone have been used in the field of implant dentistry to classify the bone at the implant site. This classification defines four types of bone being class I almost all cortical-type bone, and class IV an all trabecular bone.

The first step to place a DI involves tissue injury in the mucosa lining the edentulous ridge and the ridge itself during the osteotomy process. The traditional steps at this stage are incision of the mucosa, elevation of the mucosal flap/periosteum and perforation of the cortical and cancellous bone at the site of the placement. Finally, a DI is inserted at the recommended torque. At this point, there is an inflammatory local response as a result of the trauma caused that leads to removal of the damaged areas around the DI and preparing the site for the reparative process that will take place afterwards. With current osteotomies protocol, the canal created for the insertion of the implant is narrower than the implant itself. This helps to achieve what it is called “primary stability”, situation described as an almost lack of mobility of the DI after insertion as a result of the intimate relation between the bone and DI surface to prevent the formation of fibrous tissue that would prevent osseointegration. This also leads to a phenomenon called “press-fit”, a process by which compression of the bone neighbouring the DI leads to microfractures, collapse of vessels and a compromise in the nutrition of the bone. Although initially this would have a negative impact in the surrounding bone, it would also initiate the wound healing process.

Once the DI has been placed, different healing routes are followed depending on the nature of the bone involved. In the cortical aspect of the osteotomy, the non-vital mineralised tissue is removed before new bone starts forming. In this type of bone, new bone is formed in the surface of the old bone approaching the implant surface. This is what is known as "distance osteogenesis" (Roberts, 1988) and it has been the classical healing process followed in the first generation of DI (machined surface). In this process the trauma causes haemorrhage that eventually leads to clot formation. Cessation of circulation at the broken ends of the fragments causes local ischemia and necrosis due to the lack of oxygen supply for the osteocytes. This process leads to a cascade of signalling factors and feedback mechanisms that will cause clot degradation by leukocytes. At this point, a process of angiogenesis starts from the post-capillary venules in combination with mesenchymal cells migrating from the surrounding tissue will eventually to the formation of connective tissue that will be the precursor of osteoid bone. As it gradually mineralises it transform into immature bone, woven bone, and the process of osseointegration occurs. Conversely to this type of healing, there is another way in which healing can occur at an implant site which is called "de novo" bone formation. In this process, differentiating osteogenic cells with migratory capacity colonise the implant surface and matrix formation begins at that point in a process similar to the one described above. Therefore, distance osteogenesis will result in bone approximating the implant surface while contact osteogenesis results in bone apposition to the implant surface. The timing of this process could be summarized as follows:

Early bone formation at the DI site is not evident until days 5–7 (Berglundh, Abrahamsson, Lang, & Lindhe (2003); Colnot et al., (2007)) and it is consistent with the sequence of appositional matrix deposition and calcification from the lamina limitans of host bone onto the implant surface (Marco, Milena, Gianluca & Vittoria, 2005). Most of the interfacial zone is occupied by provisional matrix rich in collagen fibrils and vasculature, and woven bone can be observed around the vascular areas by day 7 (Berglundh et al., 2003). Through continuous deposition, trabecular bone fills the initial gap and arranges in a three-dimensional network at day 14 (Franchi et al., 2005). After 28 days, delineated bone marrow space and thickened bone trabeculae with parallel-fibered and lamellar bone can be found within the interfacial area. After 8–12 weeks, the interfacial area appears histologically to be completely replaced by mature lamellar bone in direct contact with titanium (Berglundh et al., 2003).

1.3 STRATEGIES TO ENHANCE OSSEOINTEGRATION.

As DI developed further, simplification of surgical protocols, optimisation of clinical times and shortening of healing periods became one of the main objectives to make this modality of treatment widely available not only to the general public but also more accessible to dental practitioners. All these goals seemed to share one common pathway to be achieved, shortening of the OI process. The different strategies adopted from this point onwards could be widely divided in three main categories: those directed towards the development of the implant surface, DI chemistry, and those focusing in the surgical aspect of DI placement.

1.3.1 Regarding the implant surface, there are two main ways in which DI surface can be altered. One group of techniques consist of adding material on the bulk metal (additive process); thus, a surface with "bumps" will be created in contrast to techniques where particles are removed (subtractive process). Electropolishing, mechanical polishing, blasting, etching and oxidation are examples of subtractive techniques whereas hydroxyapatite and other calcium phosphate coatings, titanium plasma-sprayed surfaces and ion deposition are other examples of additive procedures. As a result of these techniques, DI surfaces can be differentiated in topography roughness and chemical properties. Wennerberg & Albrektsson (2009) divided surface roughness into four categories:

- Smooth surfaces: Sa value <0.5 microns
- Minimally rough surfaces: Sa value 0.5–<1 micron
- Moderately rough surfaces: Sa value 1– <2 microns
- Rough surfaces: Sa value ≥2 microns.

In this aspect, several studies have pointed that DI with moderately rough surfaces provide a higher implant-to-bone contact and secondary stability when compared to smooth and rough surfaces (Buser, Schenk, Steinemann, Fiorellini, Fox & Stich (1991); Wennerberg, Albrektsson & Lausmaa (1996)). The reasons for this enhanced OI process seem to be related to the surface energy and distortional strain. Surface energy is directly related to grain size, meaning that the smaller the grain size the higher the surface energy is. This seems to have a positive impact in cell adherence (Kim et al., 2008). Regarding distortional strain, Kieswetter demonstrated that while osteoblastic cells show a cuboidal shape with polarized nuclei, the inactive bone-lining cells tended to have a flattened morphology without polarization (Kieswetter, Schwartz, Dean & Boyan, 1996). Later studies performed by Andreykiv demonstrated that "minor distortional strain and low compressive hydrostatic stress on mesenchymal stem cells were most likely for promoting osteogenic differentiation, whereas excessive distortional strain resulted in fibrogenesis as well as chondrogenesis, due to significant hydrostatic pressure" (Andreykiv, van Keulen & Prendergast, 2008). According to Schwartz, mesenchymal cell size of about 5–12 microns in length, surface microtopographic, pits with a 4-micron diameter and 1.5 micron depth are thought to be optimal for cells to attach and subsequently differentiate on the implant surface (Schwartz et al., 1999). However, reproducible surface roughness on a nanoscale level is difficult to achieve, thus optimal surface nanotopography for rapid osseointegration is still not achievable (Le Guehennec, Soueidan, Layrolle & Amouriq, 2007).

1.3.2 Regarding the DI chemistry, when a DI is placed at the recipient site, the first interactions that occur are with water molecules. Depending on their arrangement, the DI surface properties would vary. When the DI surface is very reactive, it binds to water molecules (stronger that hydrogen-bonds of ice) in a dissociated or associated state. This type of surface is called hydrophilic or wetting surfaces. However, when this type of bond is weaker than hydrogen bonds in ice, this surface type is called non-wetting or hydrophobic. This will have an impact in the subsequent adherence of different proteins, meaning that the hydrophilic/hydrophobic nature of the DI surface will determine which portion of the surrounding proteins will bind with the surface. A highly hydrophilic surface is more likely to bind with the hydrophilic area towards the surface and vice versa (Lundström, 1985). Consequently, the mixture of these proteins and their arrangement influenced by the DI surface will eventually determine the final properties of the DI surface. These days highly hydrophilic surfaces seem to be more desirable than hydrophobic ones because of their interactions with biological fluids, cells, and tissues (Buser et al., (2004); Zhao et al., (2005)) seem to lead to a more optimal OI process. Conversely, there may also be also some negative stimuli than can impair/prevent OI of DI such as corrosion products leading to an allergic-like type of reaction.

A second mechanism by which the surface chemistry may affect the cells, is the release of ions or molecules that are able to penetrate the cell membrane and/or activate some receptors. These can be widely divided into two groups: inorganic molecules and complex organic molecules. In the inorganic group, the coating of the DI surface with calcium-phosphate (CaP) has been the main one used. The biologic rationale behind this approach is that it is known that following implantation, the release of CaP into the peri-implant region increases the saturation of body fluids and results in the precipitation of a biological apatite onto the surface of the implant (Daculsi, Laboux, Malard & Weiss, 2003). This has been considered to favour osteogenic cell attachment and growth and faster OI (Davies, 2003). However, there has been some reservations in the use of these DI due to the possible delamination of then coating from the surface of the titanium implant leading to implant failure (Tinsley, Watson & Russell 2001). However, Lee, Rouhfar & Beirne (2000) conducted a systemic review that did not show that long-term survival rates were inferior for plasma-sprayed CaP coated dental implants compared with other types of dental implants.

In the group of organic molecules, we have several ones that have been studied:

- *Bone morphogenic proteins (BMPs),* are considered part of the growth factor group and belong to the transforming growth factor beta (TGFbeta) superfamily. These molecules have proven to be able to differentiate multipotent cells into an osteogenic lineage (Chen, Zhao & Mundy 2004), being BMP-2 and BMP-7 the most researched ones.

- *Platelet-derived growth factors (PDGF)* are another type of molecules that have demonstrated to have a positive impact in the OI process. They seem to have a potent mitogen and chemotactic effect in cells of mesenchymal origin, including periodontal ligament (PDL) cells and osteoblasts (Oates, Rouse & Cochran,1993), stimulate

angiogenesis and plays a crucial role in the healing of soft and hard tissue (Hollinger, Hart, Hirsch, Lynch & Friedlaender, 2008). PDGF has dimeric form (-AA, -AB, -BB, -CC, and -DD), being PDGF-BB the most widely used isoform due to its capability to bind to all known PDGF receptor isotypes (Hollinger et al., 2008). Regarding all the properties mentioned before, several studies have been conducted to better understand the intricacies of biological processes that lead to an enhanced healing response. Cho, Gerstenfeld & Einhorn (2002) demonstrated that PDGF "plays an indirect role in osteogenesis by recruiting and expanding the osteogenic cell populations, and subsequent differentiation of those cells is achieved by BMPs". Giannobile et al. (1996) also demonstrated that application of PDGF to denuded tooth root surfaces increased the proliferation of PDL cells, osteoblasts, and perivascular cells, and accelerate alveolar bone regeneration. Nevins et al. (2005) showed that the application of PDGF would also promote periodontal defect regeneration. In addition, combination with other molecules have been studied to assess possible synergistic properties.

- *Combination of PDGF and insulin-like growth factor-1 (IGF-1)* had shown to stimulate bone regeneration around the press-fit titanium implants (Lynch, Colvin & Antoniades, 1989). On the other hand, the possible inhibitory effects to osteogenesis have also been documented. Kono et al. (2007) reported that PDGF treatment negatively regulates osteogenic differentiation, and Tokunaga et al. (2008) demonstrated that specifically the PDGF receptor beta had a determinable effect on mesenchymal cell differentiation. It seems that this difference originates in the way that PDGF is delivered, meaning that pulse PDGF application stimulates osteogenesis while continuous PDGF exposure elicits an inhibitory effect (Hsieh & Graves, 1998).

- *Other growth factors and combinations have been studied such as transforming growth factor beta (TGF-b), insulin-like growth factor (IGF), and fibroblast growth factor (FGF).* TGF-b is thought to have osteoinductive properties (Macdonald, Cheung, & Anseth, 2007) but also seem to promote chondrogenesis rather than osteogenesis (Ng et al., 2008). IGF-1 and IGF-2 regulate the bone formation process (Giustina, Mazziotti & Canalis, 2008) and FGF-2 "promotes mitogenesis and reduces apoptosis of osteoprogenitor cells, which increases the population of functional osteoblasts, but induces apoptosis in more differentiated osteoblasts, thus limiting the early increase of mature cells in the osteoblast pool" (Marie, 2003). Several growth factors are involved in the OI process, therefore it makes sense to think that these have an impact among each other. Therefore, combinations of these growth factor may be another strategy to maximise OI and reduce healing times. One of the first studies heading in this direction was performed by Lynch et al. (1989) in which it was demonstrated the synergistic effects on wound healing using a combination of PDGF-BB and IGF-1. Patel et al. (2008) proved that the combination of angiogenic and osteogenic growth factors promoted bone regeneration and dual delivery of BMP/TGF-b or BMP/FGF also enhanced osseointegration in vivo (Sumner, Turner, Urban, Virdi & Inoue, 2006).

1.3.3 Regarding the surgical technique. As we mentioned previously, the traditional technique described to place DI involved placement in a fully healed alveolar ridge (6 months) after dental extraction. Many studies have described the different processes that occur at the extraction site once the tooth is removed (Araujo, Sukekava, Wennstrom y Lindhe, (2005); Schropp, Wenzel, Kostopoulos, & Karring (2003)). Histological analysis showed that at one week, the inner surfaces of the buccal and lingual walls are lined with bundle bone, being their most crestal regions formed solely by bundle bone. At this point the buccal wall is more pronounced than the lingual wall and presence of osteoclastic activity takes place in the outer aspects of this crestal region. The internal portion of the extraction socket is occupied by coagulum, granulation tissue, provisional matrix and small amounts of newly formed bone. The granulation is located at the coronal segments of the socket and the provisional matrix was the dominating tissue within the socket. This includes fibroblasts, newly formed vessels and collagen fibres. In the apical portions of the socket, small islands of newly formed woven bone are present. At the second week, mucosa of the site presents almost no sign of inflammation, but it is rich in fibroblasts and connective tissue. The crestal region of the lingual hard-tissue wall loses the bundle bone whereas in the buccal counterpart, 0.2-0.4mm of bundle bone still remains. The outer portions of the crestal region of both bone walls are still lined with osteoclasts and they are also found on the outer surface of the buccal and lingual bone walls apical of the crestal region. Large amounts of newly formed bone occur in the apical and lateral portions of the extraction socket. Provisional matrix tissue is still present in the central and marginal compartments of the socket. At the fourth week, no bundle bone can be found in the crestal region of the bone walls. However, in the crestal region of the buccal wall, a large portion of the lamellar bone is replaced with woven bone with signs of active remodelling. In addition, multitude of osteoclasts are detected on the outer surface of both the buccal and the lingual bone walls apical of the crestal regions. The lingual bone wall from this point onwards will remain consistently coronal to its buccal counterpart. Regarding the socket, provisional matrix tissue was presented in the most central portions of the socket and mineralized tissue and bone marrow occupied the remaining segments of the site. At eight-week interval, the lingual bone wall is wider than the buccal wall and crest of the buccal bone is located about 2 mm apical to the crest of the lingual hard tissue wall. At this point, a wide zone of mineralized tissue bridged the buccal and lingual bone walls of the extraction socket. The internal portion of the socket region is mainly filled with bone marrow but includes few trabeculae of mineralized tissue that is comprised of woven bone and lamellar bone. After this process, it has been estimated that around 5 to 7 mm of horizontal or buccolingual ridge reduction, representing about 50% of the initial ridge width, occurs over a 6- to 12-month period. Most of these changes occur during the first 4 months of healing (Schropp et al., 2003). In an apico-coronal direction, a reduction of 2.0 to 4.5 mm accompanies the horizontal change. This change seems to be greater when multiple neighbouring extraction are performed (Lam, 1960). This rate and pattern can be altered in the presence of pre-existing pathological process or trauma to the bone caused as a result of the extraction process. As a result of this, clinical studies were developed to assess the impact of immediate /early placement in bone dynamics.

Quite recently, description and adoption of DI placement after dental extraction instead of waiting 6 months with the consequent bone loss has shown to be a viable option. **The rationale behind using an immediate placement of DI** is based on the fact that the time and number of surgical procedures can be shortened, that some studies state that bone can be preserved at the extraction site (Werbitt & Goldberg, 1992) and that ideal aesthetics can be achieved (Werbitt & Goldberg, 1992). However, no conclusions can be drawn from the literature as there are other clinical studies that claim that bone resorption as a result of the extraction process cannot be prevented (Araujo et al., (2005); Boticelli, Berglundh & Lindhe (2004)) and aesthetics outcomes may not be as good as claimed in early studies (Chen, Darby, & Reynolds (2007); Tonetti et al., 2017). Several classifications have been proposed to define the timing in which DI is inserted (Chen & Buser (2009); Hämmerle, Chen & Wilson (2004); Wilson, (1993)). There is some variation in the way the studies define the DI period but most of them seem to agree that immediate placement occurs immediately following dental extraction, delayed placement refers to a period between 4-8 weeks and late placement after 8 weeks.

1.4 GUIDED BONE REGENERATION.

The concept of guided tissue regeneration (GTR) was first mentioned by Nyman and Karring in a series of studies performed between 1980 and 1984, although something similar called “compartmentalization” was earlier described by Melcher (1976). The principle of this technique was the selection of cells that would populate the periodontal/bony defect to encourage the proliferation of certain type of tissue. Nyman and Karring observed that regeneration of loss tissue as a result of periodontal disease could be achieved by favouring the migration of cells from the periodontal ligament and bone marrow into the defect and preventing others, mainly from soft tissues, by the use of a membrane as a mechanical barrier. This was called GTR. Soon after this, the same principle was applied in other areas such as bone regeneration. “Guided Bone Regeneration” (GBR) has been proven to be a safe and predictable in animal (Dahlin, Gottlow, Linde & Nyman, 1990) and human studies (Lang, Bragger, Hammerle & Sutter, 1994). In all animal experiments, a similar basic pattern of bone formation was repeated. Initially, trabeculae of woven bone proliferated into the defect but in some studies connective tissues was formed prior to mineralised bone. This seemed to indicate, as quoted by the investigators, that formation of new mineralised bone depended on the size of the defects and biomechanical stability. Instead, an intermediate tissue with appropriate mechanical properties would arise before ossification in those areas with tensile forces (Dahlin et al., 1990). Common to all these experiments was the finding that the bone volume increased with time and that the primary intramembranous trabecular scaffold underwent intense remodelling. Regarding human studies, there is not much published apart from a study from Hammerle, Schmid, Olah & Lang (1996) where bone healing in the lower molar region was described. For this study, hollow titanium test cylinders measuring 3.5 mm outer diameter, 2.5 mm in inner diameter and a height of 4 mm were placed into standardized holes in the retromolar area of healthy volunteers. The cylinders were placed in such a way that 1.5 to 2 mm of the test devices was submerged below the level of the surrounding bone, and 2 to 2.5 mm surpassed the bone surface. The bone-facing ends of the devices were left open. The soft tissue flaps were sutured for primary healing. After observation times ranging from 2 to 36 weeks, the cylinders along with the regenerated tissue were harvested and analysed. The tissue generated at 2 and 7 weeks exhibited a cylindrical shape, whereas the specimens harvested at 12 weeks and at later time points, yielded the form of an hourglass. Specimens of 12 weeks and less healing time almost entirely contained soft tissue. Specimens with generation times of 4 months and more contained both soft tissue and increasing amounts of mineralized bone. Up to a period of 6 months of healing, new bone was primarily filling the previously prepared defect within the host bone. Therefore, by reaching the level of the surrounding host bone, true regeneration of bone had occurred. Interestingly, bone formation did not come to a halt at this point but proceeded above the borders of the skeleton, thereby altering the genetically determined form of the mandible. This formation of new bone beyond the skeletal borders by applying the method of guided tissue regeneration was first demonstrated on the calvaria of rabbits (Schmid, Hammerle, Stich & Lang, 1991).

Subsequently, these findings were confirmed in other experimental animals such as rats (Kostopoulous & Karring, 1994), and dogs (Jovanovic, Schenk, Orsini & Kenney, 1995). Furthermore, neoformation of bone beyond the skeletal borders can also be achieved by the combined use of bone substitutes and membranes as demonstrated by Hammerle et al. (1997) and Schmid et al. (1997).

1.4.1 Types of membranes.

One of the key factors for the bone to regenerate is the preservation of the necessary space under the membrane for proliferation of new bone. This space could be maintained by having either a membrane that is rigid enough to avoid collapsing into the defect or the use of a block/particulated graft under it. Before describing the different types of membranes used in GBR procedures, it is critical to understand the main characteristics that these should have to favour the desired type of healing. These are:

- Biocompatibility. Membranes should not cause any negative reaction with the host's tissues.
- Cell-occlusion properties. Membranes should be able to prevent the migration of those cells that may impair regeneration in the area of interest.
- Integration with the host's tissue to remain stable and degrade at the expected rate to allow bone regeneration.
- Space-making capacity. Membranes should be able to maintain the space needed for the formation of new bone.

Overall, membranes can be divided into 2 main categories:

- *Non-resorbable*. The main characteristic of these membranes, as their name indicate, is that they do not resorb naturally and therefore they need to be removed in a second intervention. Expanded polytetrafluoroethylene (ePTFE) membranes are the ones that have been used the most for periodontal and GBR purposes. They are composed of a chemically stable and biologically inert polymer that resists microbiologic and enzymatic degradation and does not elicit any immunologic reactions. A titanium mesh is added within the membrane to make it more stable, easier to adapt and enhance its space-maintenance properties. The fact that it needed to be removed in a second intervention and that some undesirable side effects were commonly reported (mainly membrane exposure), caused a shift towards the second type of membranes described below.
- *Bioresorbable*. Several materials have been tested but the main ones are synthetic polymers or natural ones (Xenogeneic collagen type I or III). The way in which membranes degrade depend on several factors such as temperature, local ph, etc. and therefore the function of the membrane is variable. However, this type of membranes should remain active long enough during the healing process and at the same time not to cause adverse tissue reaction as a result of their degradation.

When it comes to performance, several studies have compared the efficiency of these type of membranes to elucidate which one would report better clinical outcomes. Hurzeler, Quinones & Schupbach (1997) compared non-resorbable e-PTFE membranes with synthetic bioresorbable membranes made of poly d-l-lactide-co-trimethylencarbonate. As quoted by the author, "significantly more bone was formed around implants covered with e-PTFE membranes, although both test and control implants exhibited new direct bone-to-implant contact". However, the reason why the performance in these resorbable membranes was worse was due to the lack of stiffness and space-making capacity of bioresorbable membranes, which tended to collapse and occlude the space available for bone regeneration. That is the reason why nowadays a scaffold or graft is used below these resorbable membranes. Experimental studies comparing non-resorbable and collagen resorbable membranes, with and without the use of a scaffold, have shown similar bone regenerative outcomes for the non-resorbable membranes and the collagen resorbable membranes when used with a scaffold (Hurzeler et al., 1998). Rothamel et al. (2004) compared different collagen membranes to assess their biodegradation and concomitant tissue integration. It was concluded that the non–cross-linked porcine-derived collagen types I and III exhibited good tissue integration, rapid neoangiogenesis, and almost complete biodegradation four weeks after implantation. The vascularization and biodegradation of chemical and enzymatically cross-linked collagen membranes, however, were slower and the resorption rate was directly related to the degree of cross-linking. Therefore, the choice of membrane material usually depends on the amount of bone regeneration needed, mainly in the vertical dimension. E-PTFE barrier membranes have demonstrated more favourable results when compared with resorbable devices, mainly due to their better space-making capacity, longer barrier function, and lack of a resorption process that may negatively affect bone formation. Nevertheless, a high rate of soft tissue dehiscence was observed with the use of ePTFE membranes. When this complication occurs, early contamination of the exposed membrane usually jeopardizes the regenerative outcome (Hämmerle & Jung, 2003).

As already mentioned, these frequent complications and the need for a second surgery to remove the membrane made resorbable membranes the current gold standard, provided they are used with an adequate space-making graft material. The choice of non–cross-linked resorbable collagen membranes should be based on their advantages in terms of earlier neoangiogenesis, lack of inflammatory response, and fast biodegradation/integration within the host tissue.

1.4.2 Types of grafting material.

These days grafting materials are classified depending on their origin. It is very important to appreciate these differences as their origin has an impact in their properties and therefore in their indications/contraindications for various dental procedures.

- *Autogenous graft:* Graft is harvested from the same individual who receives it. Traditionally considered the gold standard due to its osteoconductive, osteogenic and osteoinductive properties (Yukna, 1993). Can be harvested as a block or in particulate form. The main disadvantage is that in some cases there is limited availability, it

resorbs quick and when harvested in large quantities (as a block) there are some comorbidities associated.

- *Allograft:* Bone grafts harvested from cadaver donors and processed by freezing or demineralization and freezing. Demineralized freeze-dried bone allografts (DFDBAs) have shown osteoconductive as well as osteoinductive properties due to the release of BMPs during the demineralization process. However, there is some concern regarding their absolute non-infectivity, although there have been no reported cases of disease transmission from DFDBAs used for dental purposes.

- *Xenografts* are graft biomaterials of animal origin, mainly bovine, porcine, and equine. These graft materials are deproteinized to completely remove the organic component and thus avoid any immunogenic reaction. Their main characteristic is their osteoconductive properties and they are usually presented in a particulate form.

- *Alloplasts.* These are synthetic bone substitutes that include different combinations of calcium phosphates fabricated under different sintering conditions, which yields different physical properties and resorption rates. The combination of hydroxyapatite and beta-tricalcium phosphate (β-TCP) provides a scaffolding function (hydroxyapatite) as well as osteoconductive properties. These biomaterials are usually resorbable and delivered as granules. They should be always used in combination with barrier membranes.

1.4.3 Strategies for dehiscence-type defects, fenestration-type defects and vestibular gap between DI and bone in immediate DI placement.

The use of immediate DI presents some additional areas for consideration quite specific to the nature of this approach, such as how to manage the potential gap between the DI surface and the bony walls as a result of the discrepancy in the diameter of the extraction socket and the implant itself or any potential damage of the alveolar socket. This could, in theory, have a negative impact in the OI process as depending on the width of this defect, either OI or formation of fibrotic tissue could take place. Therefore, consideration ought to be given to the potential use of grating/membrane materials to favour the healing by filling this gap.

The use of xenografts and autografts has demonstrated excellent results in combination with membranes for dehiscence and fenestration defects. According to a systematic review published by Jensen & Terheyden (2009), the survival rates of DI placed in conjunction with augmentation of dehiscence-type defects or fenestration-type defects was 95.4%. These were comparable with survival rates of DI placed in pristine bone. In the same review, it was also concluded that fenestration-type defects resulted in 54% to 97% resolution of the former defects (mean 81.7%), and complete defect fill was reported in 68.5% of the cases. In contrast, very limited resolution of the defects could be observed when no augmentation was performed. Irrespective of the grafting protocol, complete defect fill could not be predictably

accomplished. In addition, no difference was noted whether a resorbable or a non-resorbable membrane was used to cover the defect area. However, the use of a membrane seemed to increase the augmented volume as compared to when no membrane is used. Finally, comparable results were obtained regarding implant survival and amount of defect fill when a non-resorbable membrane alone, autogenous particulate, or deproteinized bovine-bone mineral (DBBM) was used to cover dehiscence-type defects and fenestration-type defects.

Regarding the gap/defect expected between DI and bone in immediate DI placement, consideration ought to be given to the potential use of grating/membrane materials to favour the healing by filling this gap. Paolantonio et al. (2001) installed implants either in sites with healed bone (control sites) or in fresh extraction sockets (test sites). In the extraction sites, a gap ≤2mm consistently occurred between the bone walls and the implant surface, while at the control sites the cortical bone was in direct contact with the implant. For each patient, a test and control implant were retrieved after 12 months of healing. Bone-to-implant contact was very similar in both groups. In this study, no membranes or fillers were used. In a case series performed by Wilson, Carnio, Schenk & Cochran (2003), they stated that uneventful OI occurred even with gaps were 4mm and above. In this case, connective tissue membrane was used, and primary closure was achieved. Other studies (Lang, Hammerle, Bragger, Lehmann, & Nyman, 1994) stated that this hard tissue fill could occur even if transmucosal healing was performed as long as a barrier membrane was used. In addition, there is another concern with immediate DI as mentioned in previous chapters, this is the resorption of the facial bone wall. Less resorption seems to occurs when the gap between the facial bone wall and the implant is filled with a low-substitution biomaterial such as demineralized bovine bone mineral, in preclinical studies (Caneva et al., 2012) and clinical (van Steenberghe, Callens, Geers, & Jacobs, 2000).

1.5 SOFT TISSUE GRAFTING.

Soft tissue position and morphology around teeth is determined by three main factors: connective tissue attachment, bone level and presence/morphology of neighbouring teeth. When a tooth is extracted, the trauma caused would lead to bone resorption and soft tissue recession/collapse into the socket unless prevented. Therefore, reconstruction of the ideal morphology or attempt to minimise alteration after a dental extraction may require the use of hard and/or soft tissue grafting. The type of graft used in these augmentation procedures can be from various sources, each of which presents some advantages and disadvantages that make them suitable for different clinical scenarios:

- *Autogenous subepithelial (ACTG)*: The donor site is the patient's palate from which the ACTG is obtained. Evidence shows that augmented sites with ACTG at the time of implant placement have better aesthetics and thicker peri-implant tissues (Esposito, Maghaireh, Grusovin, Ziounas & Worthington, 2012). This type of graft is considered today the gold standard to which any new material is compared with.

- *Allografts:* Acellular dermal matrix (ADM) have been used around teeth and implants to substitute the autogenous connective tissue grafts, especially for larger recipient sites or when obtaining autogenous tissue is not feasible and would lead to much higher postoperative discomfort. Allografts and autografts yield similar predictability for root coverage techniques; however, connective tissue autografts result in superior defect coverage, higher keratinized tissue and attachment gain, and lower residual probing depths (Hirsch, Goldstein, Goultschin, Boyan & Schwartz, 2005).

- *Xenografts:* These include thick collagen matrices have been introduced as an alternative to autografts or allografts for use as free gingival or connective tissue grafts. They are made of type I and III porcine collagen without further cross-linking or chemical treatment. The advantages of this material are less morbidity, facilitation of clot stabilization and the subsequent soft tissue ingrowth, reduction of surgical time, unlimited availability and natural soft tissue colour and structure. However, according to evidence these materials although able to augment soft tissues around DI, they seem to present poorer aesthetic outcomes (Esposito et al., 2012).

Other strategies have been reported with the aim to correct soft tissue deficiencies mainly at gingival recessions such as biologic agents, GTR, platelet-rich fibrin (PRF) or living cellular constructs. However, these were not reported in this introduction as our research made use of techniques aimed at increasing soft tissue volume mainly.

1.6 FLAPLESS SURGERY.

Further consideration has been given in recent years to the impact of flap elevation in the bone resorption process and outcome of DI, particularly in the aesthetic zone. Pfeifer (1965) performed histological examination of block biopsies taken after the extraction of several teeth. Either apically repositioned flap or split flap procedure was performed on each volunteer before the extractions and biopsies were obtained in subsequent visits. Biopsies were taken from a different patient each time at 4, 7, 14 and 21-day intervals. It was shown that osteoclastic activity occurred in the apically repositioned flap, mainly in the crestal area and along the gingival tissue surface of the alveolar process. On the other hand, very little osteoclastic activity was seen in split flap procedures where a thick layer of tissue was covering the bone. Severe osteoclastic activity was seen in those areas were the bone was nicked in preparation of the flap or were the periosteum was inadvertently removed. Based on this, they concluded that avoiding elevation of a full-thickness flap would have a positive impact in bone remodelling, preventing some of the resorption caused by bone denudation. When immediate DI placement using a flapless approach was tested in the dog model (Blanco, Nunez, Aracil, Munoz & Ramos, 2008), they concluded that "flapless immediate implant surgery produced a significant reduction in the vestibular biologic width and a minor reduction in buccal bone plate resorption". Recent systematic reviews looking into the impact of a flapless approach for the placement of DI in bone levels and survival rates (Lin, Chan, Bashutski, Oh & Wang, 2014) concluded that survival rate and radiographic marginal bone loss of flapless intervention was comparable with the flap surgery approach. This was achieved after thorough pre-surgical planning and by expert surgeons, factors that need to be accounted for. However, not all the included studies in the systematic review achieved the same outcomes and other studies reported an increased amount of bone loss in the flapless group due to limited visualisation of the surgical field and not ideal implant placement (Malo & Nobre, 2008), therefore a conclusive statement could not be made. Besides, it was mentioned that the overall results stated in this review could not be applied to flapless immediate DI placement due to the conflicting results in this subgroup. In a recent prospective study that looked at bone volume changes in implant placement with/without flap elevation, it was concluded that there was no significant association between initial buccal bone width and ridge width at six months and there were no statistically significant differences between the flapless/flap protocols, although more ridge reduction was observed for the flap group (Mazzocco et al., 2017).

1.7 PROVISIONAL RESTORATION OF DI.

Once the clinician and the patient have agreed to replace a missing/failing tooth with DI, there are several stages where provisionalisation could take place:

- Phase I. Provisionalisation immediately after tooth extraction until implant placement.
- Phase II. From implant placement to abutment connection, prior to loading.
- Phase III. From abutment connection to final crown/ bridge placement, with loading of the implant and the development of the emergence and mucosa profile.

As mentioned in previous paragraphs, DI have been traditionally restored/loaded after 3-6 months to allow OI to happen. During this period, a temporary restoration/prosthesis is normally fabricated to allow function, maintain aesthetics (when tooth loss occurred in the aesthetic region) and preserving the prosthetic space by preventing tilting/supraeruption. In addition, these temporary restorations could be really helpful to create an emergence profile that it appears natural and in harmony with surrounding tissue when maximising aesthetics is of vital importance. However, apart from functional aspects and helping with soft tissue management, temporary restorations could generate information that is critical to the final prosthetic design as they should allow for the evaluation of static and dynamic variables that help confirm the diagnosis and definitive prosthetic design such as ideal vertical dimension, development of the occlusal scheme, aesthetics/phonetics and laboratory communication. Traditionally, these temporary restorations could be divided as follow:

1.7.1 Removable (tooth/soft tissue borne) prosthesis:

- Removable prosthesis (RPD): The main advantages of this modality of treatment is that RPDs are simple to construct, relatively inexpensive, and easy for the surgeon or restorative clinician to adjust and fit. Patients that require staged treatment with serial extractions may have teeth added to their existing removable dentures with minimal cost. However, they may reduce the effectiveness of any additional surgical bone and gingival augmentation procedure used to optimize the implant site if too much pressure was placed on the supporting tissues during the healing phase. Therefore, care must be taken to prevent the gingival portion of the provisional partial denture from contacting the healing soft tissue or an exposed healing abutment.
- Essix retainer: This prosthesis is made from an acrylic tooth bonded to a clear vacuform material on a cast of the diagnostic wax up. The prosthesis provides protection to the underlying soft tissue and implant during the healing phase. Limitations of this provisional restoration include its inability to mould the surrounding soft tissue, and lack of patient's compliance can cause rapid occlusal wear through the vacuform material. However, some patients may not like to wear, or are unable to tolerate, a removable provisional prosthesis, thus fixed provisional prosthesis are sometimes necessary.

1.7.2 Fix prosthesis:

These types of prostheses are supported by adjacent teeth or implant in a fixed manner. Some of the different approaches based on this concept are described below:

- Fixed tooth supported provisional restorations in the upper anterior region include the use of orthodontic brackets and archwire on several teeth adjacent to the edentulous region.
- Resin bonded provisional pontic, which are tooth-supported and retained by acid etching the neighbouring teeth.
- Temporary DI: Transitional implants are loaded immediately to support the provisional restoration. They can be used to support fixed restorations or to retain complete mandibular dentures.
- Supported by DI after placement: Provisional restorations may be used at the time of implant placement or after an appropriate healing period. The term “immediate restoration” is used when a prosthesis is fixed to the implants within 48 hours without achieving full occlusal contact with the opposing dentition, whereas “immediate loading” is when the prosthesis is fixed to the implants in occlusion within 48 hours. The concept of immediate implantation and provisionalisation for replacing single teeth in the premaxilla comes with some obvious benefits as it combines tooth extraction, implant surgery, and restorative treatment. Thus, the time gain can be optimized with the subsequent reduction in the number of procedures and overall treatment time. At least, from a theoretical point of view, hard and soft tissues may be maximally preserved, since there is only one surgical phase and a provisional restoration offers an instant mechanical support to the papillae and midfacial gingival tissues. Slagter et al. (2014) reported “minimal changes in peri implant hard/soft tissues as well as excellent survival/success rates in DI immediately placed and provisionalised in the aesthetic region”. Block et al. (2009) found that immediate/delayed placement and immediate restoration had similar responses in bone levels, but immediate restoration prevented 1 mm of apical migration of the gingival margin. Evidence shows that the survival rates of DI that are immediately restored range from 93%-100% (Cornelini, Cangini, Covani, & Wilson (2005); Ferrara, Galli, Mauro, & Macaluso (2006); Tsirlis (2005)) and that the success rate is at least comparable to data published for single-tooth implants placed according to the standard protocol in healed sites.

1.8 OUTCOME EVALUATION.

1.8.1 Survival/success rate.

Implant survival has been traditionally used as a primary outcome measurement because it provides long-term data on the predictability of OI. It has been one of the most common ones used in implant dentistry, making comparisons between different studies and power calculations relatively straightforward. Implant survival has been traditionally used as a primary outcome measurement because it provides long-term data on the predictability of OI. It has been one of the most common ones used in implant dentistry, making comparisons between different studies and power calculations relatively straightforward. However, there are several limitations associated with this specific outcome (Needleman, Chin, O'Brien, Petrie, & Donos 2012), such as:

- The presence or absence of the implant in the patient's mouth per se may not be associated with the maintenance or re-establishment of the patient well-being (psychosocial characteristics and quality of life, absence of disease, function, aesthetics).
- Lack of consensus of how to define implant survival. Although well-defined criteria exist, not all studies use the same one, creating some limitations when comparing studies with different criteria.
- The reported high survival rates require large sample size and/or long-term follow-up for clinical research.

Implant success is another outcome commonly reported in the literature. Conversely to DI survival that fundamentally reports whether a DI is in function in the mouth without any obvious problems, implant success goes a step further and takes into account (depending on the criteria used) other elements such as progressive bone loss, disease of peri-implant mucosa and, more recently, aesthetics and patient reported outcomes. However, as pointed by Needleman et al. 2012, consensus has not been reached for "success", with several authors providing their own criteria (Albrektsson et al. (1986); Carr Wolfaardt & Garrett (2011); Misch et al. (2008)). Therefore, the lack of a universally accepted success criteria makes the interpretation and comparison of the data between studies extremely difficult and constitutes a problem in the implant dentistry literature in general (Ong et al., 2008). Despite of the limitations outlined above, the use of "Albrektsson Criteria" is one of the most widespread criteria used among studies (Needleman et al., 2012).

1.8.2 Aesthetic evaluation. PES/WES indexes.

As mentioned in previous chapters, DI patients have moved from merely functional expectations ("having a fixed tooth to chew instead of a denture") to a more holistic one in which other aspects, such as aesthetics, are considered equally important. However, no objective tool was available in those early days to measure "aesthetics", this been a subjective evaluation with the consequent difficulties to achieve consensus about what should be expected. Since, several methods have been used to assess this aesthetic element. One of the first ones was the level of "mucosal margin" in relation to the contralateral natural tooth (Andersson, Odman y Carlsson 1995), using the cemento-enamel junction as reference. Papilla height/embrasure fill adjacent to DI has been also assessed (Grunder (2000); Jemt (1997)), leading to the publication of several studies looking into different ways to maximise papilla fill due to the importance of this structure in the final aesthetic outcome of final restoration (Choquet et al. (2001); Tarnow et al. (2003); Tarnow, Cho & Wallace (2000); Tarnow, Magner, & Fletcher (1992)). Changes in soft tissue morphology has been also evaluated due to the importance of having enough volume to make a restoration look natural, particularly in those areas where a deficit is expected. Finally, colour of gingiva and restoration compared to contralateral tooth has been also assessed as this would have an obvious impact in DI aesthetics. This match can be challenging, mainly due to the different nature of natural tooth structures (enamel, dentine) and restoration materials. All these approaches were quite valid and a positive step forward in assessing aesthetics. However, they seemed to lack completeness in the sense that they evaluated some specific aspects of dental aesthetics but ignoring others that were equally important. This is probably the greatest feature of the PES index developed by Fürhauser et al. (2005) as an amalgam of aesthetics elements that were graded together rather than individual features. The aim of this test was to obtain an objective aesthetic evaluation of the soft tissues and this was achieved by rating seven features in relation to soft tissues aesthetics. This test was originally performed by dental practitioners from different specialties and the authors reached the conclusion that it reflected accurately and in a reproducible manner aesthetics of the soft tissue around single implants or natural teeth. Belser et al. (2009) modified Fürhauser test to assess tooth aesthetics in relation to surrounding tissues. This modification included the reduction in number of items to analyse (five instead of seven) and was called "White Aesthetic Score (WES)".

Of all aesthetics tests mentioned above, PES and WES seems to be the more objective indexes, demonstrating the highest repeatability among all objective aesthetic evaluation methods (Tettamanti et al., 2016).

1.8.3 Hard tissue evaluation.

When immediate DI technique was firstly proposed, the main aim was avoiding resorption of the buccal plate in the vertical and horizontal dimensions. However, evidence showed that it still occurred after immediate placement as seen in preclinical (Araujo & Lindhe (2009); Araujo et al. (2005); Botticelli et al. (2004)); and clinical studies (Covani, Canullo, Toti, Alfonsi & Barone (2014); Sanz et al. (2010)). Therefore, identification of potential factors that may prevent/increase this resorption process as well as elucidating the rate in which this resorption process occurs would be beneficial to manage this element more efficiently, mainly in aesthetic areas. According to current evidence, there are not many studies that have been able to look into this resorption process of the buccal plate due to the limitations of traditional radiographic imaging to assess this structure three-dimensionally and the ethical issues that may arise from elevating a flap from a DI that is already osseointegrated and in function. Recent studies seemed to have overcome this problem by the use of newer cone beam computed tomography (CBCT) imaging at different time intervals (Benic et al. (2012); Kuchler, Chappuis, Gruber, Lang & Salvi (2015); Mazzocco et al. (2017)) due to its wider availability and less radiation used in modern CBCT machines.

1.8.4 Patients' reported outcomes (PROMs).

Traditionally, treatment outcomes in implant dentistry have been always evaluated from a clinician perspective via survival/success rates, aesthetic outcomes, etc. However, patient reported outcomes (PROMs) are becoming increasingly more important as it is the patient who will ultimately judge how successful the treatment has been regardless the clinician's perspective. Den Hartog, Slater, Vissink, Meijer & Raghoebar (2008) performed a systematic review looking at different outcome measures used to evaluate the clinical outcome of immediate and conventional DI supported single-tooth restorations in partially edentulous patients. It was concluded that few reports included data regarding aesthetic outcomes, soft-tissue aspects, and patient's satisfaction. This conclusion was also highlighted in the VIII European Workshop where the main topic of discussion was clinical research in implant dentistry. One of the main conclusions was that patient's reported outcomes were under-reported and these should be included in future studies (Lang, Zitzmann & Periodontology, 2012).

II. PhD JUSTIFICATION AND HYPOTHESIS.

Since the development of DI, various flap designs have been used with the aim to allow access to the underlying bone. However, as this discipline developed and more emphasis was gradually put in dental aesthetics, flap design had to follow this trend, particularly in those areas where achieving good aesthetics was critical. The elevation of a mucoperiosteal flap has been always associated with important advantages for the dental surgeon such as:

- Good visualisation of the surgical field.
- Better assessment of the bony morphology.
- Easiness in the placement of DI.
- Identification of buccal fenestrations or dehiscences during implant placement.
- Flap mobility for passive advancement in the coronal direction. This would allow better closure over the socket, grafting material and membrane if needed.

However, this elevation is always associated with an increased morbidity of the procedure, bone remodelling (Pfeifer, 1965) and the potential negative impact in final soft tissue position. As a result of these limitations, the concept of "flapless placement" was introduced (Sclar, 1999). This approach brought several advantages such as less morbidity, reduction of surgical times/appointments, preservation of vascular supply and potentially reduction of remodelling processes. If this flapless approach was used with an immediate DI placement, better results would be expected not only clinically (due to improved vascularization and less remodelling), but also a better patient's experience (due to a reduced number of appointments and less morbidity during DI placement). Due to the ambiguity, scarcity and low quality of most of published literature regarding flapless technique in immediate DI, it was found appropriate to focus this PhD in the design and development of a randomised controlled trial to investigate a flapless approach technique in the placement of DI and how it compares with the conventional approach involving elevation of a mucoperiosteal flap. This is a very relevant area that deserves careful attention as the elevation of a mucoperiosteal flap will invariably cause bone remodelling (Pfeifer, 1965) and therefore may have a negative impact in the final aesthetic outcome. Of all the bony areas exposed during a mucoperiosteal flap elevation, it is the change that occur in the buccal plate that have a greater impact in the final outcome due to the connection between the thickness of this structure and the final position of the gingival margin. Therefore, better understanding of the changes that take place in this specific structure after implant placement and how these could be managed to optimise aesthetics would have a major and significant positive impact in this type of treatment. In an attempt to explore these changes, intraoperative measures of the buccal plate and a CBCT at 12 months after DI placement were planned as part of this PhD investigation in order to assess how flap elevation vs. a flapless approach may affect the thickness of the buccal plate and how this translated in the final position of gingival margin and final aesthetics.

Based on all exposed above, the aim of this study was testing the main null hypothesis that there were no differences in survival/success rate in a group of patients requiring single immediate DI in the anterior maxillary region treated with a flapless vs. flap approach against the alternative hypothesis of a difference. For the secondary outcomes, the study tested the null hypotheses that there were no differences in PES, cortical plate resorption and PROMS in a group of patients requiring single immediate DI in the anterior maxillary region treated with a flapless vs. flap approach against the alternative hypothesis of a difference.

III. AIMS OF THE STUDY

3.1 Primary aim:

To compare the survival and success rate for immediate DI placed in the anterior/premolar region of the maxilla using a flapless vs. flap approach with simultaneous soft/hard tissue grafting.

3.2 Secondary objectives:

- To compare final aesthetics regarding soft tissue and final restoration, using PES and WES indexes, in immediate DI placed in the anterior/premolar region of the maxilla using a flapless vs. flap approach with simultaneous soft/hard tissue grafting.

- To compare resorption/remodelling of buccal plate for DI placed in the anterior/premolar region of the maxilla using a flapless vs. flap approach with simultaneous soft/hard tissue grafting.

- To compare patient's satisfaction and perception of final aesthetic result for DI placed in the anterior/premolar region of the maxilla using a flapless vs. flap approach with simultaneous soft/hard tissue grafting.

IV. MATERIALS AND METHODS

4.1 MATERIALS.

4.1.1 STUDY DESIGN.

This study was a randomized, controlled, parallel-arm, blind, university-based study designed to compare the clinical, radiographic, aesthetic and patient-reported outcomes of immediate DI placed with a flap vs. flapless approach in the maxillary anterior and premolar region. The study was primarily reviewed and approved by the Universidad de Murcia Ethical Committee and competent local authorities (Study ID: 1738/2017*,* ***Annex 1***). All study procedures were performed in accordance with the principles of the Declaration of Helsinki.

4.1.2 SAMPLE CALCULATION, SELECTION/EXLUSION CRITERIA AND RANDOMIZATION.

For sample size calculation, advice from statistician was sought. A sample of 15 patients per arm was suggested. To compensate for missing data and attrition, a sample size of 20 patients per arm were recruited. Adult subjects in need of a single tooth extraction in the anterior region of the dentition (including premolars) for trauma, periodontitis, endodontic or unrestorable caries were invited to participate in this study. Information sheets (***Annex 2***) were given to the patients and consent was gathered if patient decided to participate in the study (***Annex 3***).

The following exclusion criteria was applied during the recruitment process.

(i) Patient did not have relevant medical conditions, such as uncontrolled diabetes (Fiorellini, Chen, Nevins & Nevins, 2000), had not received head and neck radiation for cancer treatment or current treatment with intravenous Bisphosphonates. Radiation of head/neck has been reported to decrease success rate of DI up to 40% (Granström, Tjellstrom & Branemark (1999); Granström, Tjellstrom, Branemark & Fornander (1993); Lindquist, Rockler & Carlsson (1988)). For many years, it was reported that osteoradionecrosis (ORN) was due to vascular derangement and hypoxia of bone cells caused by the tissue-damaging effects of radiation. Based on this hypothesis, it has been recommended that oral surgical procedures in patients at risk of ORN be performed in conjunction with hyperbaric oxygen (HBO) therapy. Granström et al. (1999) reported that use of HBO therapy improved implant survival rates. However, the value of HBO therapy for the management of ORN has been called into question. A systematic review by Coulthard, Patel, Grusovin, Worthingto & Esposito (2008) indicated that there is no high-quality evidence that HBO therapy improves implant survival in irradiated patients.

(ii) Only non-smokers included. Evidence shows that smokers seem to be more prone to periodontitis and peri-implantitis (Lindquist, Carlsson & Jemt, 1997) as well as implant loss (Strietzel et al., 2007). The mechanisms involved seem to be related to an altered immune response (Kinane & Chestnutt, 2000) and alteration in wound healing (Labriola, Needleman & Moles, 2005).

(iii) Patient had completed periodontal treatment in presence of active periodontitis. The association between self-performed oral hygiene levels and peri-implantitis has been shown to be dose-dependent (Ferreira, Silva, Cortelli, Costa & Costa, 2006). This study demonstrated that in "partially edentulous patients with very poor and poor oral hygiene are at statistically significantly higher risks of developing peri-implant mucositis and peri-implantitis compared with patients with proper plaque control".

(iv) Patient presented with full mouth plaque (FMPS) and bleeding scores (FMBS) equal or below 25% at study baseline for the reasons mentioned in the previous paragraph. Bleeding scores have shown to reflect in the long-term compliance of oral hygiene. Individuals with low mean bleeding on probing (BoP) percentages (<10% of the surfaces) may be regarded as patients with a low risk for recurrent disease (Lang, Adler, Joss & Nyman, 1990), while patients with mean BoP percentages of >25% should be considered to be at high risk for re-infection.

(v) Patient did not have clinically symptomatic periapical radiolucencies, acute abscesses or chronic sinus tracts at the site of extraction. Some studies have reported a higher occurrence of periapical lesions at DI when the tooth replaced had exhibited periapical pathology, or when the tooth next to the implant site exhibited periapical pathology. Lefever, Van Assche, Temmerman, Teughels & Quirynen (2013) performed a retrospective study to evaluate whether an endodontic pathology on the extracted tooth or adjacent teeth of an implant site had an influence on the emergence of a periapical lesion. They found that if an endodontic treatment or a periapical lesion at the apex of a tooth was present, a periapical lesion around the implant can be detected in 8.2% up to 13.6% (OR 7.2). For periapical pathology at the adjacent teeth, the percentage rises to 25% (OR 8.0). Based on this, they concluded that "when an endodontic pathology is present on the extracted or neighbouring teeth, it is significantly more likely that a periapical lesion will develop around a future implant".

(vi) Patient had adequate quantity of native bone to achieve primary stability.

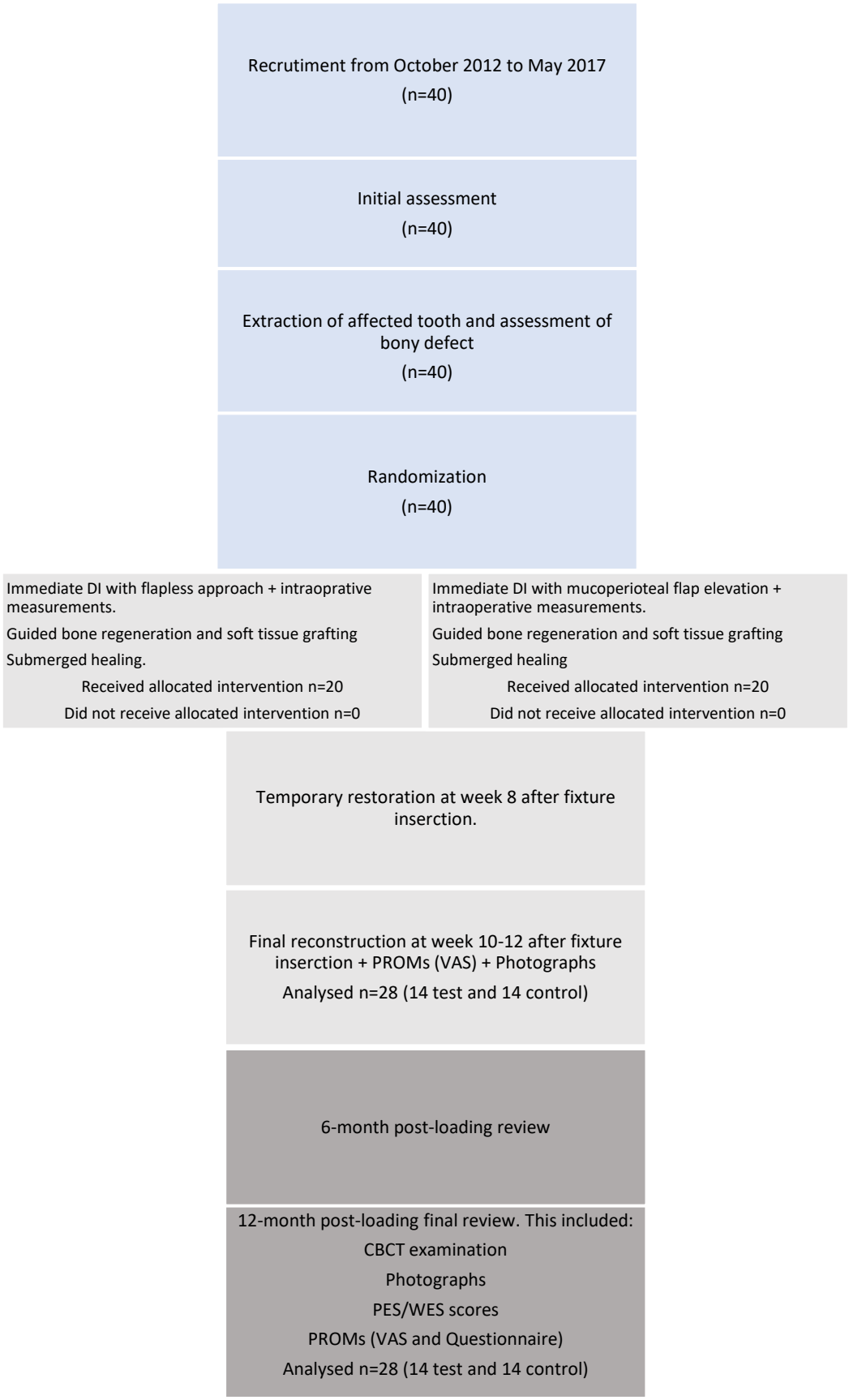
(vii) Patient had an adequate mesio-distal space for implant placement (≥6.5 mm, i.e. 1.5 mm on each side of the 3.5 mm platform).

(viii) Patient was available for follow-up according to protocol for 12 months post-loading to be able to assess the results of the proposed investigation.

Patients recruited received the allocated treatment from April 2018 to May 2017. In all subjects entered in the study, immediate DI placement was feasible. Due to time limitations for data collection and elaboration of this PhD, 14 test and 14 controls were included in the study from the total sample (20 tests and 20 controls). A total of 40 subjects were randomized and received the allocated treatment.

Randomization was done by balanced block randomization using a computer-generated table with random numbers. Treatment assignment was concealed to the treating surgeon by opaque envelopes that were opened only after completion of tooth extraction and final assessment of the feasibility of immediate implant placement. Clinical/radiographic measures, aesthetic evaluations and statistical analyses were performed blind with respect to treatment assignment.

Figure 1: *Consort diagram.*



4.2 METHODS.

Self-tapping, screw-shaped Biomimetic OCEAN, Avinent® implants of different lengths and diameters were immediately placed after dental extraction. The surface of this DI was hydrophilic, moderately rough with the addition of calcium-phosphate to the titanium oxide. These properties seemed to be ideal to promote OI (Subira-Pifarre et al., 2019).
In all study cases, test and control, discrepancies between the extraction socket and the implant surface were filled with a mix of bone replacement graft (Gen-Os, Osteógenos s.r.l.) and autologous bone, covered with a collagen membrane (Evolution, Osteógenos, s.r.l). In addition, soft tissues were augmented by the use of ACTG. Treatment was provided at the Dental department of University of Murcia.

4.2.1 STUDY INTERVENTIONS.

Before any surgical procedure was planned, a baseline full-mouth periodontal examination was performed using a UNC15 periodontal probe. This included probing pocket depth (PPD), gingival recessions (REC), clinical attachment level (CAL) and bleeding on probing (bop) in six points per tooth, excluding third molars. Besides, intraoral photographs and radiographic examination were performed prior to the extraction of the affected tooth to evaluate hard tissues in the area of interest. Once all the information needed was gathered, patient was further assessed against the inclusion/exclusion criteria and arrangements for the clinical intervention were made.

Before surgery, all subjects were premedicated with Amoxicillin/Clavulanic acid or Clindamycin (if patient had an allergy to penicillin) and a new periapical radiograph was taken if needed. Luxation of the affected tooth was performed with fine periotomes and forceps attempting to avoid trauma to the alveolus. After extraction and before opening the randomization envelope, the surgeon verified the feasibility of immediate implant placement on the basis of absence of acute infection or purulence and presence of an adequate quantity of alveolar bone to allow immediate implant placement with primary stability. At this stage, surgeon proceeded as indicated in the envelope by placing the DI with a flap or flapless approach. ***Figure 2*** shows an example of DI placement in the test group and ***Figure 3*** in the control group.

Figure 2. DI placement test group.

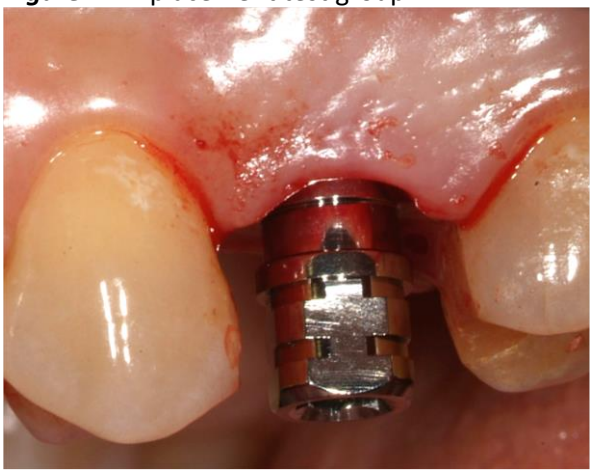
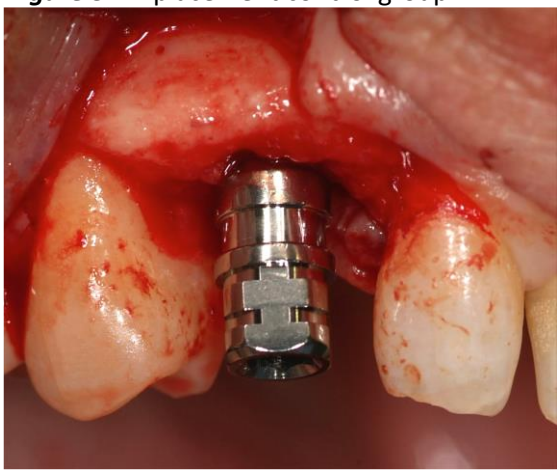


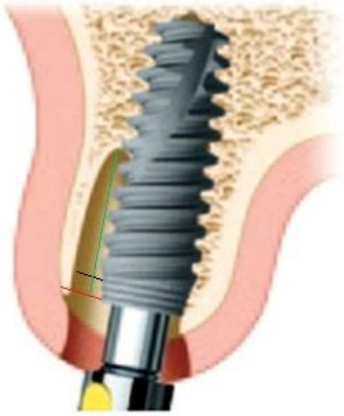
Figure 3. DI placement control group.



Intraoperative measures were taken after DI placement to assess bone levels (vertically and horizontally) at the edentulous site. Specifically, the following distances were measured and recorded for every patient ***(Figure 4):***

- Distance between DI surface (mid buccal) and inner aspect of the buccal cortical plate *(black line in figure 4).*
- Distance between DI surface (mid buccal) and external aspect of the buccal cortical plate *(red line figure 4).*
- Distance between DI shoulder (mid buccal) and first bone-to-implant contact *(green line figure 4).*

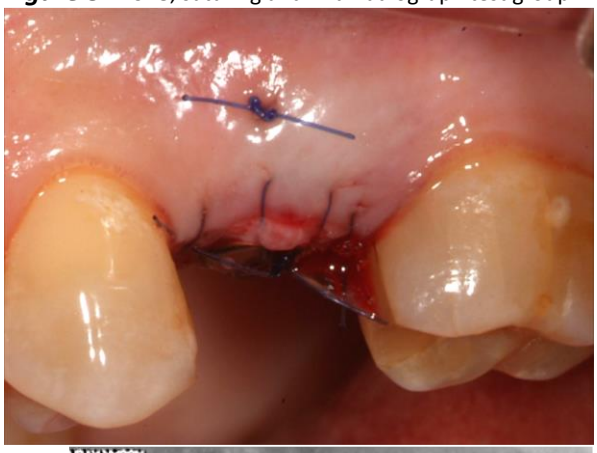
(*) Figure 4: Intraoperative bone measurements.



(*) ***Image source.*** *Oral health Group (https://www.oralhealthgroup.com/).*

For both treatment groups, implant placement and implant diameter choice were restoratively driven to maximize aesthetics and function. Bone replacement graft consisting of a 1/1 proportion mix of autograft/xenograft (Meijer, Slagter, Vissink & Raghoebar (2019); Nimwegen et al., (2018)) in combination with a resorbable collagen membrane (porcine/equine origin) were used in all cases to fill the horizontal gap between DI and bone. ACTG was also used in all cases to increase the thickness of vestibular soft tissues at the location of DI (examples in ***Figure 5, Figure 6***). At this stage, a submerged healing was attempted and abutment of the same diameter or narrower than the DI was placed to allow more space for the horizontal development of the soft tissues, favouring support for the formation of new papilla and minimising the vertical collapse of the newly formed soft tissue (Salama, Salama, Garber, & Adar, 2015). This approach was favoured due to the limited impact that immediate restorations seem to have in final position of soft tissues (Block et al., (2009); Slagter et al., (2014)). Once suturing was completed, post-op radiograph and photographs were taken. Post-operative medications included continuation of the antibiotic regimen for 5 days, a second dose of diclofenac or paracetamol, and twice daily chlorhexidine 0.12% rinsing for the first 2 weeks.

Figure 5. ACTG, suturing and final radiograph test group



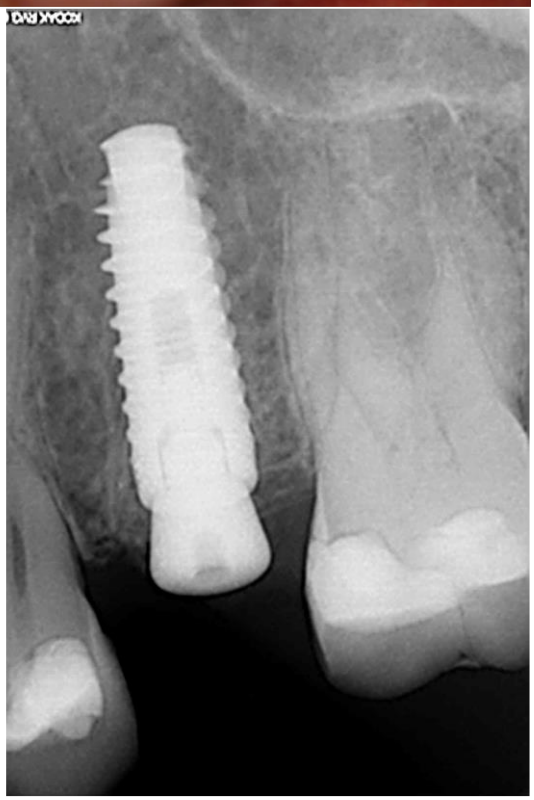
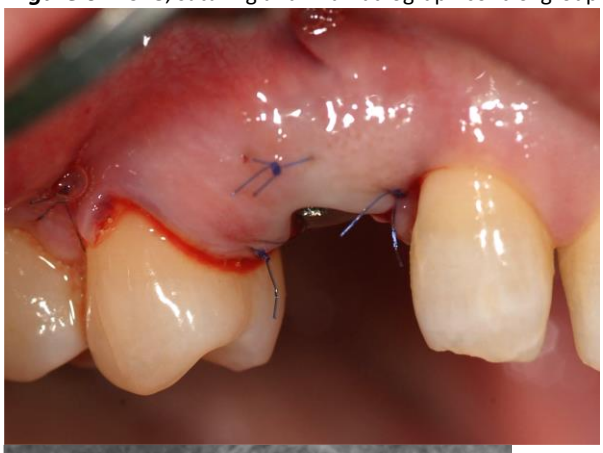
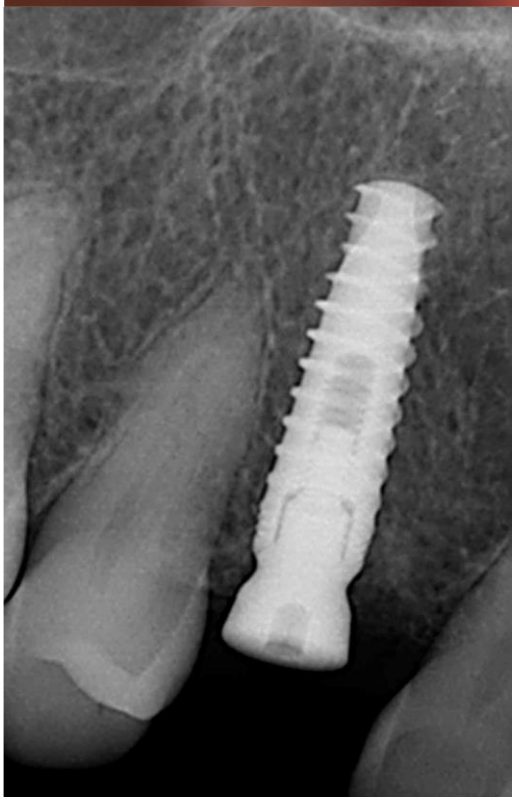


Figure 6. ACTG, suturing and final radiograph control group





Sutures were removed 1 week after the procedure. At this stage, oral hygiene was assessed by using a disclosing agent (Plac-Control®, DENTAID, Barcelona, Spain), oral hygiene instructions were given accordingly, and any adverse events were recorded. Patients were instructed to avoid chewing or trauma to the treated area for the first 2 weeks. Normal oral hygiene and chewing was resumed by week 3. Post-surgical controls consisting of professional tooth cleaning and oral hygiene instructions were performed at weeks 3, 9 and 12.

Temporary implant-supported reconstruction was initiated between weeks 8-10 after DI insertion to allow contouring of peri-implant soft tissues (examples in ***Figure 7*** and ***Figure 8***). At this visit, occlusion was adjusted to have light contact on the DI-supported restoration on intercuspal (IC) position and during lateral/anterior guidance when DI restoration was involved. This restoration was screw-retained.

Figure 7. Temporary restoration test group.

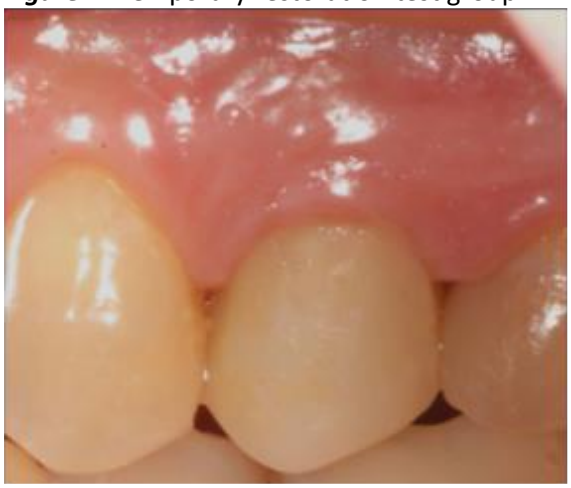
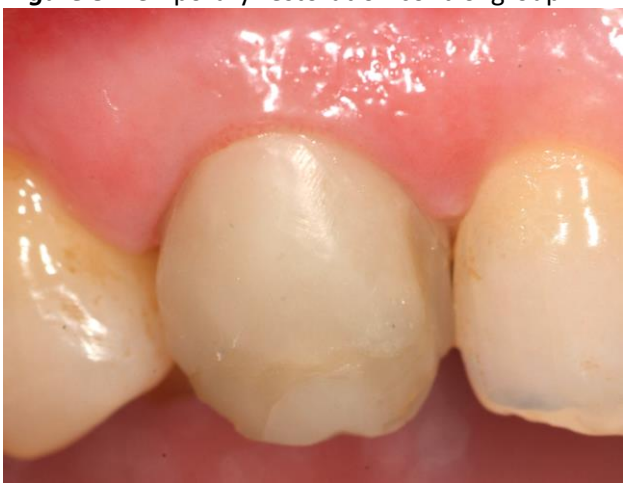


Figure 8. Temporary restoration control group.



Final reconstruction was initiated at week 10-12 after DI insertion and fitted at week 12-14 (examples in ***Figure 9*** and ***Figure 10***). At this visit, restoration was placed, cleansability was assessed and finally fitted at a torque of 20 n/cm. Occlusion was adjusted to have light contact on DI-supported restoration on IC, lateral guidance and anterior guidance when restoration was involved. Standardised photographs of implant suprastructure/surrounding tissues and periapical radiograph were taken, and any adverse events recorded.

Figure 9. Final restoration test group.

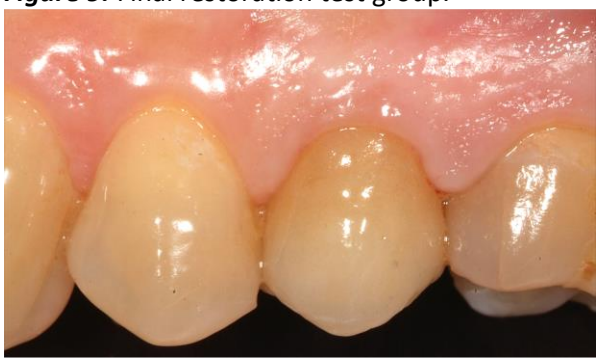


Figure 10. Final restoration control group.

Review was performed at six-month post -loading. At this visit, occlusion was checked and adjusted as needed, oral hygiene was assessed by using a disclosing agent (Plac-Control®, DENTAID, Barcelona, Spain), removal of supra/subgingival deposits performed, oral hygiene instructions given accordingly, and any adverse events recorded.

Finally, *at 12-month post-loading,* all the variables and assessment provided at 6-month follow-up were repeated, a periapical radiograph and photographs were taken and final CBCT scan was performed to assess buccal plate of DI.

4.2.2 STUDY OUTCOMES EVALUATION.

4.2.2.1 DI Survival/Success.

After one year of DI loading (final assessment), DI survival and success was assessed evaluating several parameters. For DI survival, the criteria described by Albrektsson et al. (1986) was used. This criterion considers:

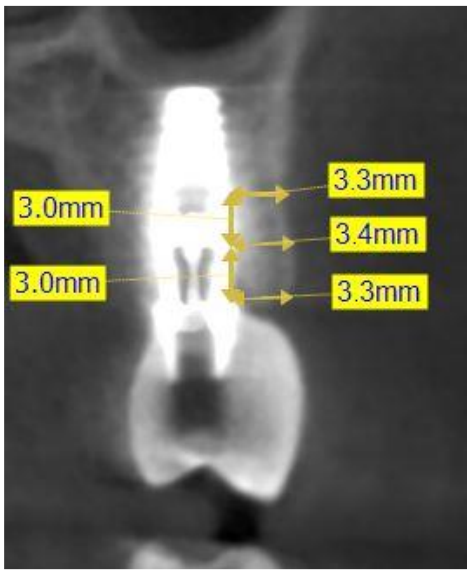
- Successful osseointegration.
- Lack of complications.
- Bone loss less than 0.2mm/year after loading.

For DI success, apart from the criteria included for survival, an additional component that considered aesthetics of DI surrounding mucosa and restoration was introduced. This was due to the importance of implant aesthetics in the anterior region. Of all available indexes, PES and WES were preferred as they seemed to be the most objectives, demonstrating the highest repeatability among all objective aesthetic evaluation methods (Tettamanti et al., 2016). For this study, DI was considered successful if survival conditions were met, PES score was 8 or above and WES score was 6 or above at the final assessment (Cosyn et al., 2011).

4.2.2.2 Hard tissue evaluation.

As mentioned previously, standardised radiographic examination was performed before the extraction of the affected tooth and the day of DI placement. In addition, standardised radiographic examination was performed when final restoration was placed and at 6 and 12 months. Finally, a CBCT examination was performed at 12-month post loading. The distance from DI surface (mid buccal) to external aspect of buccal plate measured at 0mm, 3mm and 6mm from DI shoulder at 12 months post-loading CBCT were performed by a single calibrated examiner who was unaware of the treatment assignment using the proprietary software for the Vatech 3D scanner (Ez3D) as example below ***(Figure 11).***

Figure 11: Example of hard tissue evaluation (CBCT) at 12-month post-loading.



4.2.2.3 Soft tissue evaluation. Pink Aesthetic Score (PES).

The Fürhauser test was used for the assessment of soft tissues. The aim of this test was to obtain an objective aesthetic evaluation of the soft tissues and this was achieved by rating seven features in relation to soft tissues aesthetics. A grade ranging from 0 to 2 was given for each item and a final score was obtained ***(annex 4).*** The best possible score is 14, reflecting a perfect harmony between the gingiva and the tooth/implant under evaluation. This evaluation is made by comparing the gingiva-dental/implant complex with the neighbouring tooth in the premolar region and contralateral one in the incisal and canine zone. In this clinical study, PES was performed for the test and control restorations at 12-month final assessment. Eight blinded clinicians (two periodontists, two orthodontists, two prosthodontists and two general dentists) not aware of group allocation provided their PES assessment. To evaluate the reproducibility of the assessor, all PES measurements were repeated by the same clinicians after 8-12 weeks.

4.2.2.4 White tissues (tooth) evaluation. White Aesthetic Score (WES).

Belser et al. (2009) modified Fürhauser test to assess tooth aesthetics in relation to the surrounding tissues. This modification included the reduction in number of items to analyse (five instead of seven) and was called "White Aesthetic Score (WES)" ***(annex 5).*** In the present clinical study, WES was performed for the test and control restorations at 12-month final assessment. Eight blinded clinicians (two periodontists, two orthodontists, two prosthodontists and two general dentists) not aware of group allocation provided their WES assessment. To evaluate the reproducibility of the assessor, all WES measurements were repeated by the same clinicians after 8-12 weeks.

4.2.2.5 Patients' reported outcomes (PROMs).

At 12-month post-loading review visit, the clinician providing the examination asked the following questions to the patients:

- *Do you experience any difficulties during talking?.*
- *Are you happy with the final aesthetic outcome?.*
- *Would you undergo the same intervention again?.*
- *Would you recommend this treatment to another patient?.*
- *Do you feel the implant tooth as one of your own?.*
- *How do you feel about the oral hygiene measures needed to look after the implant tooth?.*
- *How do you feel about the help provided by your dentist during the treatment?.*
- *What do you think about the cost-effectiveness of this treatment?.*

The possible answers were extremely negative, moderately negative, slightly negative, slightly positive, moderately positive and extremely positive. All the answers were recorded in a patient's form and kept in records. This questionnaire was based in the one used by de Bruyn, Collaert, Linden & Bjorn (1997) (***Annex 6***).

In addition, a visual analogue scale (VAS) was filled by the patient rating aesthetic of the restoration at the day of the fit and at 12-month review. The scale ranged from 0 (very poor aesthetics) to 10 (excellent aesthetics) (***Annex 7***).

4.2.3 STATISTICAL ANALYSIS.

Descriptive statistics were expressed as mean and standard deviation for continuous variables and frequency and percentage for dichotomous variables.

Between-group differences for PES failure and WES/PES failure scores were estimated by Fisher Exact Test for each dentist group and OddsRatio (OR) and 95% CI for OddsRatio were reported.

Mixed effect model for PES failure and PES/WES failure were created to test any differences in failure between dentist groups (GDP, Orthodontist, Periodontist, Prosthodontist) using the latter as fixed effects covariate while patients as random effects.

Comparisons between buccal plate thickness at time of DI placement (intraoperative measures) and 12-month post-loading (CBCT) within each group were made by paired t-tests, to detect any changes in buccal plate thickness over time.

Between-group differences for buccal plate thickness, PES and WES scores were estimated by an independent samples t-test.

Intra-examiner correlation coefficients (between first and second evaluation) for mean Total PES and WES score outcomes at 12 months post-loading were assessed by dentist groups (GDP, Orthodontist, Periodontist, Prosthodontist), treatment groups (flap/flapless) and overall.

Inter-examiner correlation coefficients for mean Total PES and WES score outcomes at 12 months post-loading were assessed by dentist groups (GDP, Orthodontist, Periodontist, Prosthodontist) and by treatment groups (flap/flapless).

Mixed effect model for Total PES and WES Score were created using treatment group (flap/flapless), dentist groups (GDP, Orthodontist, Periodontist, Prosthodontist), distance DI to buccal bone plate (mm) at 12 months as fixed effects covariates while measurement occasion nested examiner as random effects covariate.

Within-group comparisons for patient reported outcomes (aesthetic) between baseline and 12 months were made by paired t-tests, while between-group differences were estimated by an independent samples t-test.

The Mann-Whitney U test was used to compare differences between the two independent groups for each question of the survey (ordinal outcome).

JMP® Pro 13 was used as statistical software. All statistical comparisons were conducted at the 0.05 level of significance.

V. RESULTS

5.1 POPULATION CHARACTERISTICS AND REASONS FOR EXTRACTIONS.

Table 1 shows the patient characteristics and reason for extractions. No statistically significant differences were present between test and control groups. Good levels of oral hygiene were demonstrated (FMPS below 25%). Full-mouth plaque scores and full mouth bleeding scores as well as the number of residual periodontal pockets remained stable throughout the study period. All subjects completed the post-surgical follow-up and two subjects (one in each group) missed the 12-month follow up.

Table 1: Patient's characteristics.

	Flap [n=14] (%)	**Flapless [n=14] (%)**
Males	5 (35.72)	5 (35.72)
Females	9 (64.28)	9 (64.28)
Age at implant insertion (mean, SD)	47.43 (10.28)	47 (10.88)
Non-smokers	14(100)	14(100)
Extraction due to tooth/root fracture	6 (42.9)	9 (64.3)
Extraction due to unrestorable tooth due to extensive carious lesion.	3 (21.4)	1 (7.1)
Extraction due to endodontic pathology.	2 (14.3)	1 (7.1)
Extraction due to retained root	3 (21.4)	3 (21.5)

5.2 SURGICAL OUTCOMES.

Table 2 shows the different implant diameter, length, insertion torque, intra-operative measures, horizontal distance between DI and external aspect of cortical plate, type of grafting and origin of ACTG for test and control group. In the test group, 14 DI were placed to immediately replace 10 premolars, 1 canine and 2 lateral incisors. The diameter of the DI ranged from 3.5 to 4.5mm and lengths from 10 to 13 mm. The insertion torque ranged from 30 to 56 n/cm2. The mean horizontal distance between the DI surface and the external aspect of the cortical plate was 3.63mm. In the control group, 14 DI were placed to immediately replace 10 premolars, 2 canines and 2 central incisors. The diameter of the DI ranged from 3.5 to 4.5mm and lengths from 10 to 13 mm. The insertion torque ranged from 30 to 45 n/cm2. The mean horizontal distance between the DI surface and the external aspect of the cortical plate was 3.71mm. No complications were noted in the test or control group during the study. The main deviations from the protocol were that one patient in test group and one patient in control group did not have membrane placed as part of GBR procedure. The surgeon in charge of the placement considered that membrane was not needed to provide GBR as vestibular gap was very narrow. However, grafting of the vestibular gap was still provided for those patients. For one patient in control group and one patient in test group, 12-month post-loading pictures could not be retrieved and final CBCT could not be performed as they did not attend their appointment. These subjects were not included in the statistical analysis performed for the aesthetic and radiographic outcomes.

Table 2: Intervention characteristics.

	Flap [n=14] (%)	**Flapless [n=14] (%)**
Implants at central incisor position	2 (14.3)	0 (0)
Implants at lateral incisor position	0 (0)	2 (14.3)
Implants at canine position	2 (14.3)	1 (7.1)
Implants at 1st premolar position	5 (35.7)	4 (28.6)
Implants at 2nd premolar position	5 (35.7)	7 (50)
Implants 10mm long	1 (7.1)	4 (28.6)
Implants 11.5mm long	6 (42.9)	8 (57.1)
Implants 13mm long	6 (42.9)	2 (14.3)
Implants 15mm long	1 (7.1)	0 (0)
Mean implant length	12.29 (1.22)	11.29 (0.99)
Implants with 3.5mm diameter	3 (21.4)	2 (14.3)
Implants with 4.0mm diameter	10 (71.5)	5 (35.7)
Implants with 4.5mm diameter	1 (7.1)	7 (50)
Insertion torque below 35 n/cm	2 (14.3)	1 (7.1)
Average insertion torque (SD)	38.33 (5.40)	45.57 (7.11)
Mean horizontal distance (mm) between implant (mid buccal) and external aspect of buccal cortical plate (SD).	3.71 (1.45)	3.63 (1.32)
Mean vertical distance (mm) between implant shoulder and first BIC (SD).	3.79 (1.55)	4.32 (2.37)
Sites augmented with xenograft and membrane at implant placement	13(92.85)	13(92.85)
Site augmented with soft tissue graft at implant placement	14 (100)	14 (100)

5.3 SURVIVAL/SUCCESS RATE.

No implants failed either in the test or control group, giving a 100% survival rate for both interventions. PES/WES results were pooled according to specialist groups to calculate success rate for each treatment modality. When just PES criterion was applied, success rate ranged from 92.3% (GDP subgroup) to 100% (Pros, Perio, Ortho subgroup) in the test group and 92.3% (all subgroups) in the control group. On the other hand, when PES/WES were considered, success ranged from 69.2% (GDP subgroup) to 84.6% (Pros, Perio, Ortho subgroup) in the test group and from 84.6% (Perio subgroup) to 92.3% (GDP, Pros, Ortho subgroup) in the control group **(*Table 3*)**. Fisher's Exact test was used to test success differences within each group for PES **(*table 4)*** and PES/WES ***(table 5*)**. These differences were not statistically significant. Mixed effect model for PES and PES/WES failure were created to test any differences in failure between dentist groups (GDP, Orthodontist, Periodontist, Prosthodontist) using the latter as fixed effects covariate while patients as random effects. No statistically significant differences were estimated for PES failure (*p-value = 0.397*) and for PES/WES failure (*p-value = 0.303*).

Table 3: PES/WES Test (T) and control (C) cases below success threshold.

	PES <8	**WES <6**
General dental practitioners	C5 T2	T7, T8, T14
Periodontists	C5	C2, C5 T7, T8
Orthodontists	C5	C5 T7, T8
Prosthodontists	C5	T7, T8

Table 4: Fisher's Exact test for PES failure within each group.

	2 tail *p-value* of Fisher exact Test	**Odds Ratio [95% CI]**
General dental practitioners	1.0	1 [0.05-17.75]
Periodontists	1.0	0
Orthodontists	1.0	0
Prosthodontists	1.0	0

Table 5: Fisher's Exact test for PES/WES failure within each group.

	2 tail *p-value* of Fisher exact Test	**Odds Ratio [95% CI]**
General dental practitioners	0.32	5.2 [0.5-54.0]
Periodontists	1.0	1.0 [0.12-8.3]
Orthodontists	1.0	2.1 [0.17-27]
Prosthodontists	1.0	2.1 [0.17-27]

5.4 RADIOGRAPHIC OUTCOMES.

Table 6 reports on the comparison of buccal plate thickness at time of DI placement (intraoperative measures) and 12-month post-loading (CBCT). The mean distance from DI surface to external aspect of cortical plate measured intra-operatively was 3.5mm in control group and 3.46mm in test group *(p = 0.93)* whist the mean distance from DI to external aspect of cortical plate (at 0mm) measured in CBCT at 12-month post loading was 2.78mm in control group and 2.54mm in test group *(p = 0.60),* with a difference compared to baseline measurement of 0.72mm in control group and 0.92 in test group *(p = 0.58).* None of these differences were statistically significant.

Table 6: Comparison of buccal plate thickness at time of DI placement (intraoperative measures) and 12-month post-loading (CBCT).

	Distance from DI to external aspect of cortical plate (mm) intraoperatively.	**Distance from DI to external aspect of cortical plate (at 0mm) measured in CBCT at 12-month post loading.**	**Baseline – 12-month difference in distance from DI to external aspect of cortical plate**
	N Mean (SD) [95% CI]	N Mean (SD) [95% CI]	N Mean (SE) [95% CI]
Flap	13 3.50 (1.26) [2.74, 4.26]	13 2.78 (0.98) [2.19, 3.38]	13 0.72 (0.22) [0.25, 1.19]
Flapless	13 3.46 (1.22) [2.73, 4.20]	13 2.54 (1.37) [0.38, 3.37]	13 0.92 (0.31) [0.25, 1.60]
Difference	0.04 [-0.96, 1.04]	0.25 [0.72, 1.22]	0.21 [-0.58, 0.99]
p-value	0.9375	0.6036	0.5880

*Statistically significant difference

5.5 CORRELATION ANALYSIS.

Tables 7 and ***8*** represent the intra-examiner correlation coefficients (between first and second evaluation) for mean PES/WES outcomes at 12 months post-loading to assess operator consistency in the evaluation. Regarding PES, an overall strong intra-examiner correlation was noted for all dental groups (0.78), being orthodontists (0.88) the strongest one and general dental practitioners (GDP) (0.69) the weakest. For WES results, an overall strong intra-examiner correlation was also noted for all dental groups (0.76), being GDP (0.89) the strongest and prosthodontists (0.65) the weakest. ***Tables 9*** and ***10*** represent the inter-examiner correlation coefficients by dentist groups (GDP, Orthodontist, Periodontist, Prosthodontist) for mean PES/WES outcomes at 12 months post-loading. Overall, a weak-to-moderate inter-examiner correlation ranging from 0.22 to 0.56 was noted for PES results whereas a moderate inter-examiner correlation ranging from 0.40 to 0.55 was noted for WES results.

Table 7: Intra-examiner Correlation Coefficient for PES at 12 months post-loading.

Intra-examiner Correlation Coefficient for Total PES score (208 Ratings)			
Examiners		**Group**	
		Flap	**Flapless**
GDPs	0.69	0.68	0.71
Periodontists	0.83	0.90	0.66
Orthodontists	0.88	0.93	0.82
Prosthodontists	0.74	0.69	0.81
Overall	0.78	0.77	0.79

Table 8: Intra-examiner Correlation Coefficient for WES at 12 months post-loading.

Intra-examiner Correlation Coefficient for Total WES score (208 Ratings)			
Examiners		**Group**	
		Flap	**Flapless**
GDPs	0.89	0.91	0.87
Periodontists	0.77	0.75	0.82
Orthodontists	0.78	0.81	0.78
Prosthodontists	0.65	0.46	0.75
Overall	0.76	0.73	0.79

Table 9: Inter-examiner Correlation Coefficients by dentist groups (GDP, Orthodontist, Periodontist, Prosthodontist) for mean PES outcomes at 12 months post-loading.

Inter-examiner Correlation Coefficient for Total PES score (208 Ratings)			
Examiner	**Overall**	**Group**	
		Flap	**Flapless**
GDP - Orthodontist	0.25	0.24	0.27
GDP - Periodontist	0.43	0.47	0.45
GDP - Prosthodontist	0.22	0.44	-0.02
Orthodontist - Periodontist	0.56	0.55	0.60
Orthodontist - Prosthodontist	0.27	0.44	0.02
Periodontist - Prosthodontist	0.42	0.62	0.06

Table 10: Inter-examiner Correlation Coefficients by dentist groups (GDP, Orthodontist, Periodontist, Prosthodontist) for mean WES outcomes at 12 months post-loading.

Inter-examiner Correlation Coefficient for Total WES score (208 Ratings)			
Examiner	**Overall**	**Group**	
		Flap	**Flapless**
GDP - Orthodontist	0.40	0.33	0.45
GDP - Periodontist	0.47	0.38	0.54
GDP - Prosthodontist	0.55	0.45	0.64
Orthodontist - Periodontist	0.43	0.38	0.47
Orthodontist - Prosthodontist	0.44	0.30	0.52
Periodontist - Prosthodontist	0.40	0.28	0.47

5.6 AESTHETIC OUTCOMES.

Tables 11 *and* ***12*** report mean PES/WES outcomes at 12 months post-loading (208 ratings) with standard deviations (standard errors for differences) is in parenthesis. PES scores were essentially identical in the test and control groups although some statistical differences were noted in some items of PES scores. Regarding WES score, overall results were also quite similar between groups and no statistically significant difference was noted. Furthermore, the majority of cases had PES/WES scores greater than the arbitrarily set clinical acceptability level in an aesthetic site. Arbitrarily set of inadequate PES scores (below 8) was obtained in one test (7.7%) and one control case (7.7%) whereas inadequate WES scores (below 6) were obtained in two control cases (15.4%) and three test cases (23.1%) (***table 3***).

Table11: PES at 12 months post-loading.

	Mesial papilla	Distal papilla	Soft tissue level	Soft tissue contour	Alveolar process deficiency	Soft tissue colour	Soft tissue texture	Total PES score
Flap=13	1.69 (0.46)	1.15 (0.68)	1.67 (0.50)	1.43 (0.60)	1.67 (0.52)	1.50 (0.58)	1.44 (0.60)	10.54 (2.49)
Flapless=13	1.57 (0.59)	1.47 (0.64)	1.56 (0.60)	1.41 (0.62)	1.65 (0.52)	1.65 (0.52)	1.50 (0.61)	10.80 (2.23)
Difference	-0.12 (0.05)	0.32 (0.07)	-0.11 (0.05)	-0.01 (0.06)	-0.02 (0.05)	0.14 (0.05)	0.06 (0.06)	0.25 (0.23)
p-value	0.0210*	<0.0001*	0.0411*	0.8092	0.7057	0.0078*	0.3340	0.2725

*Statistically significant difference.

Table 12: WES at 12 months post-loading.

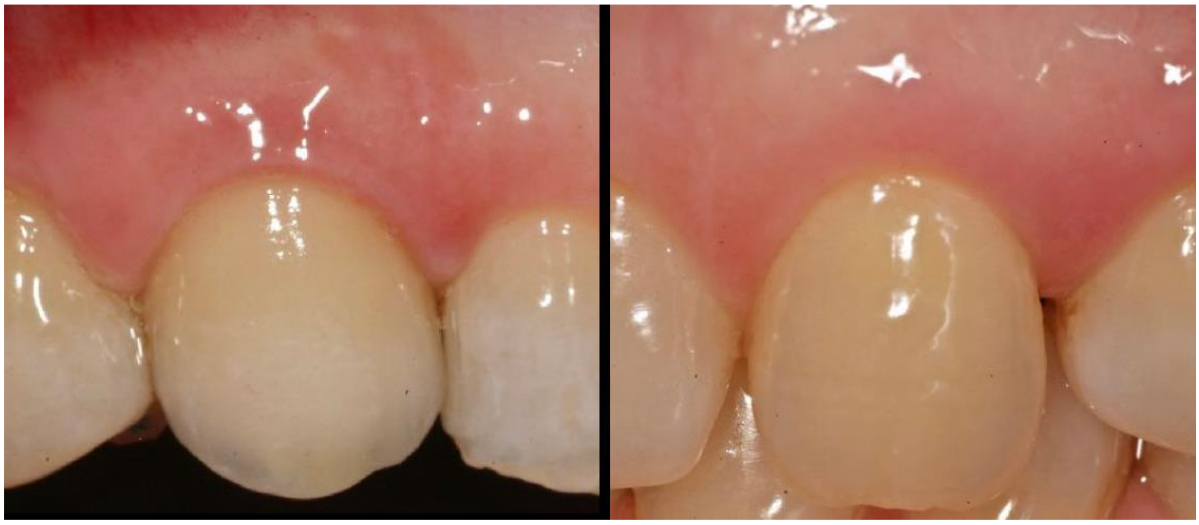
	Tooth form	Tooth volume/outline	Colour (hue/value)	Surface texture	Translucency	Total WES Score
Flap=13	1.30 (0.62)	1.25 (0.62)	1.26 (0.61)	1.64 (0.50)	1.50 (0.62)	6.97 (1.97)
Flapless=13	1.30 (0.65)	1.27 (0.69)	1.28 (0.67)	1.62 (0.53)	1.48 (0.63)	6.95 (2.40)
Difference	0 (0.06)	0.03 (0.06)	0.02 (0.06)	-0.02 (0.05)	-0.01 (0.06)	-0.01 (0.22)
p-value	1.0000	0.6556	0.7588	0.6364	0.8142	0.9466

*Statistically significant difference.

A representative example of some of the cases that obtained the highest and lowest PES/WES scores for control and test group are shown below:

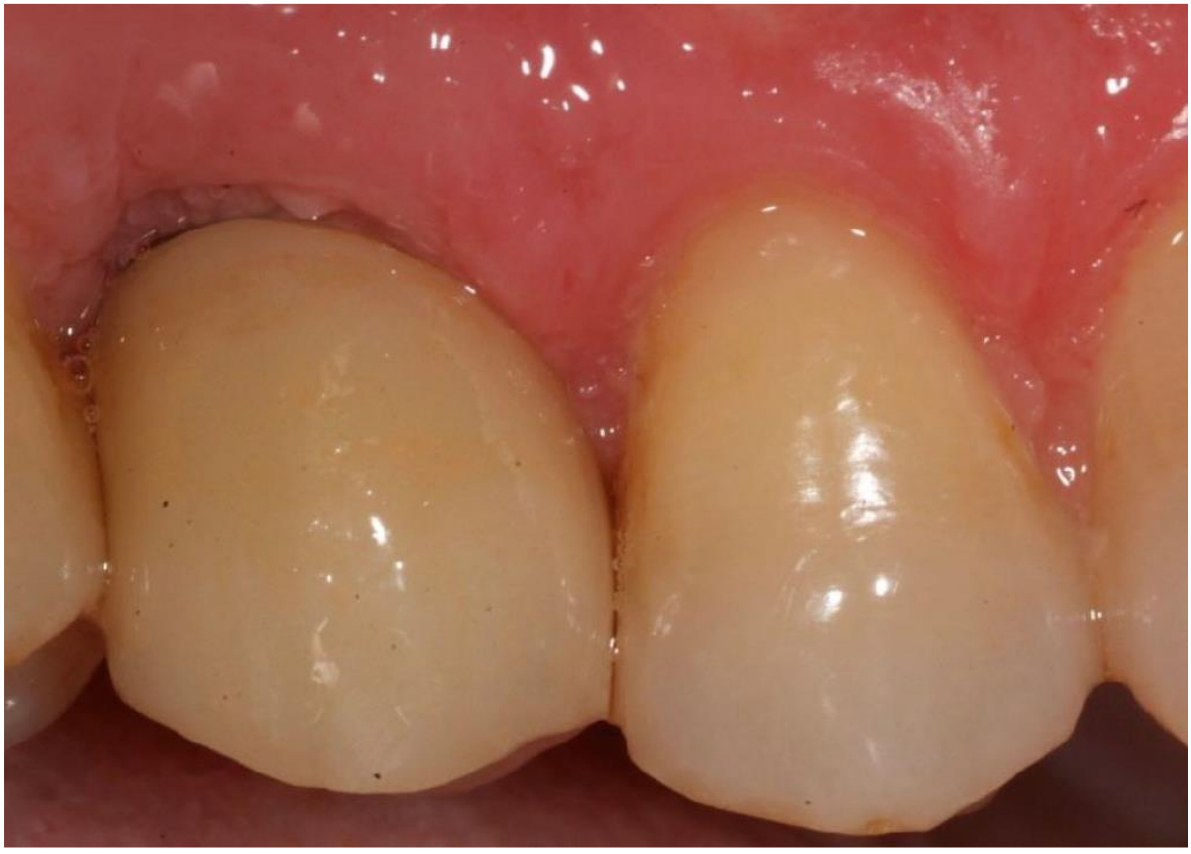
Control group:

Figure 12. High PES/WES score (PES=14; WES=9)



(13* Implant) (23* Natural tooth) *FDI notation

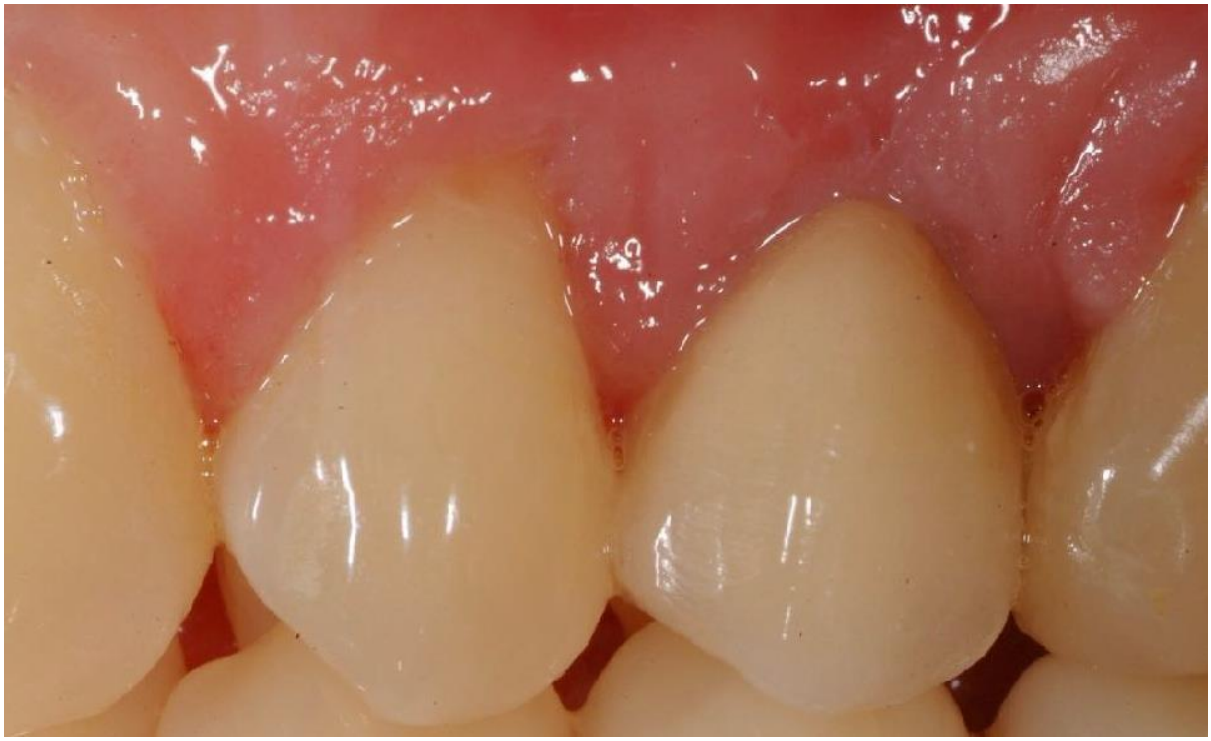
Figure 13. Low PES/WES score (PES=5; WES=5)



(15* Implant) (14* Natural tooth) *FDI notation

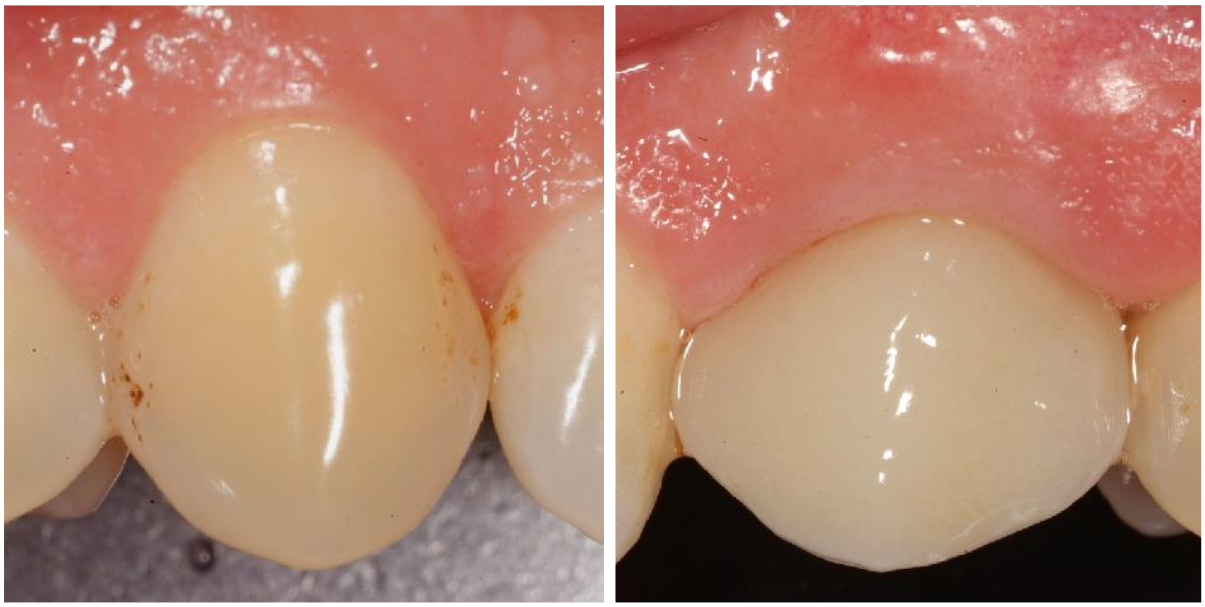
Test group:

Figure 14. High PES/WES score (PES=13; WES=9)



(14* Natural tooth) (15* Implant) *FDI notation

Figure 15. Low PES/WES score (PES=10; WES=3)



(13* Natural tooth) (23* Implant) *FDI notation

5.7 PATIENT-REPORTED OUTCOMES (PROMs).

Final DI aesthetics were evaluated using a "Visual Analog Score (VAS)" the day of the fit and at 12-month post-loading review (***Table 13***). Overall, patients' satisfaction was very high (>85%in the VAS scale for both groups at 12-month post-loading review), and no significant differences were observed comparing test and control subjects at any of the analysed intervals. Patient's satisfaction survey (***Table 14***) showed that the majority of the patients (86%) felt "slightly positive" to "extremely positive" to all the questions included in the questionnaire. No statistically significant differences were found between test/control groups apart from the question regarding "*the specific needs to clean the DI*".

Table 13: VAS day of fit and 12-month post-loading review.

	VAS at fit	**VAS at 12 months after loading**	**Fit – 12-month difference in VAS**
	N Mean (SD) [95% CI]	N Mean (SD) [95% CI]	N Mean (SE) [95% CI]
Flap	13 7.92 (1.12) [7.25, 8.60]	13 8.85 (0.90) [8.30, 9.39]	13 0.92 (0.86) [0.40, 1.44]
Flapless	13 8.77 (1.09) [8.11, 9.43]	13 9.31 (0.95) [8.74, 9.88]	13 0.54 (0.66) [0.14, 0.94]
Difference	0.85 [-0.05, 1.74]	0.46 [-0.29, 1.21]	-0.38 [-1.01, 0.24]
P-value	0.0624	0.2148	0.2147

*Statistically significant difference.

Table 14. Patients' satisfaction survey at 12 month post-loading. Differences between test and control group

Questions	**p-value**
Did you experience any difficulties with your speech?	0.7364
How do you feel about the final aesthetic result?	0.3801
Would you undergo the same procedure again?	0.7506
Would you recommend this treatment to another patient?	0.2171
Do you feel the implant as your own tooth?	0.2254
How do you feel about the specific needs to clean the implant?	0.0103*
How do you feel about the cooperation of your dentist throughout the treatment	0.4230
How do you feel about the cost benefit of this treatment	0.5476

*Statistically significant difference.

5.8 MIXED-EFFECT MODEL FOR TOTAL PES/WES.

Mixed effect model for Total PES and WES Score (***Figure 16*** and ***Figure 17***) were created using treatment group (flap/flapless), dentist groups (GDP, Orthodontist, Periodontist, Prosthodontist), distance DI – buccal bone plate (mm) at 12 months as fixed effects covariates while measurement occasion nested examiner as random effects covariate. GDP group was used reference group, so all the estimated differences were calculated against that group. Based on this, a statistically significant association was found between "Total PES Score" and Examiner (Periodontist and Prosthodontist group). Regarding "Total WES Score", no significant association was found with any of the covariates.

Figure 16: Mixed effect model output for Total PES Score.

Term	Estimate	Std Error	Prob>|t|
Intercept	9.85	0.39	<.0001*
Group[Control]	-0.25	0.22	0.2410
Distance DI - External Cortical Plate (mm) 12 month	0.023	0.09	0.8036
Examiner[Ortho]	0.13	0.40	0.7532
Examiner[Perio]	1.42	0.40	0.0236*
Examiner[Prostho]	1.97	0.40	0.0079*

*Statistically significant difference

Figure 17: Mixed effect model output for Total WES score.

Term	Estimate	t Ratio	Prob>|t|
Intercept	6.70	19.70	<.0001*
Group[Control]	0.01	0.07	0.9465
Distance DI - External Cortical Plate (mm) 12 month	-0.05	-0.52	0.6020
Examiner[Ortho]	0.61	2.08	0.1059
Examiner[Perio]	0.31	1.06	0.3501
Examiner[Prostho]	0.62	2.11	0.1020

*Statistically significant difference

VI. DISCUSSION

6.1 METHODOLOGY.

The use of immediate placement for DI in the study. As mentioned during the introduction, the use of immediate DI has several advantages over traditional/delayed placement that makes this modality of treatment quite appealing for the clinician and patient. The time and number of surgical procedures can be shortened, and ideal aesthetics can be achieved (Werbitt & Goldberg, 1992). Consequently, it was decided that this approach would be taken for the placement of DI in both groups. The main variable assessed in this study was flap design, therefore a traditional full-thickness flap was adopted for the control group vs. a flapless in the test group.

The use of flapless approach in the test group. In an early study performed in humans to test the impact of flap elevation in bone remodelling, Pfeifer (1965) concluded that avoiding elevation of a full-thickness flap would have a positive impact in bone remodelling, preventing some of the resorption caused by bone denudation. This was a very important finding as less bone remodelling meant more stable bone levels. This may have a potential positive impact in DI soft tissue aesthetics as gingival recession associated with bone loss/remodelling of the buccal plate after placement is one of the main reasons for failure in immediate DI in the anterior region (Chen et al., 2007). Besides, not having to elevate a full thickness flap may result in less postoperative comorbidities for the patient. When immediate DI placement with a flapless approach was tested in the dog model (Blanco et al., 2008), they concluded that "flapless immediate implant surgery produced a significant reduction in the vestibular biologic width and a minor reduction in buccal bone plate resorption". A recent systematic review looking into the impact of a flapless approach for the placement of DI in bone levels and survival rates (Lin et al., 2014) concluded that survival rate and radiographic marginal bone loss of flapless intervention was comparable with the flap surgery approach. However, it was also mentioned that the overall results stated in this review could not be applied to flapless immediate DI placement due to the conflicting results in this subgroup. Based on the scarcity of studies looking into flap design in immediate DI placement, it seemed justifiable to use this variable as the main one to test in this study.

The use of Biomimetic OCEAN, Avinent® DI. The surface of this DI is hydrophilic, moderately rough with the addition of calcium-phosphate to the titanium oxide. According to evidence presented in the introduction paragraph, DI with moderately rough surfaces provide a higher implant-to-bone contact and secondary stability when compared to smooth and rough surfaces (Buser et al. (1991); Wennerberg et al. (1996)). Besides, the addition of CaP has been considered to favour osteogenic cell attachment and growth and faster OI (Davies, 2003). All these findings are further confirmed by recent studies (Subira-Pifarre et al. 2019). Consequently, this type of DI had all the desirable qualities to minimise the risk of failure and was used in this study.

The use of grafting material and barrier membrane. When immediate DI approach is adopted, consideration ought to be given to the gap commonly found between the DI and the bony walls. As mentioned during the introduction, strategies should be taken to promote bone fill within this gap as well as minimising bone resorption. Less resorption seems to occur when the gap between the facial bone wall and the implant is filled with a low-substitution biomaterial such as demineralized bovine bone mineral (Caneva et al. (2012); van Steenberghe et al. (2000)). Other studies (Lang et al., 1994) stated that this hard tissue fill could occur even if transmucosal healing was performed if a barrier membrane was used. Based on all this, it was decided that the patients included in this study would receive a combination of autograft/xenograft (Covani et al. (2012); Meijer et al. (2018); Nimwegen et al. (2018)) with a resorbable collagen membrane (Hurzeler et al. (1998); Rothamel et al. (2004)) to fill the small defect between DI and bone, and any other small bony defect/deficiency detected during immediate DI procedure with the view to encourage bone formation in these defects as well as trying to minimise the amount of buccal plate resorption.

The use of ACTG. When a tooth is extracted, the trauma caused would lead to bone resorption and soft tissue recession/collapse into the socket unless prevented. Therefore, reconstruction of the ideal morphology or attempt to minimise alteration after a dental extraction may require the use of soft tissue grafting. Evidence shows that augmented sites with ACTG at the time of implant placement have better aesthetics and thicker peri-implant tissues (Esposito et al., 2012). Nowadays, this type of graft is considered today the gold standard to which any new material is compared with. Based on this, it was decided that ACTG would be used in this study for soft tissue augmentation in all test/control subjects to maximise aesthetic outcomes in both groups (Nimwegen et al., 2018).

Provisionalisation method for DI. Provisionalisation in this clinical study was provided 30-45 days after DI placement (phase II) via non-occluding, implant-supported, screw-retained restoration. This approach was favoured due to the limited impact that immediate restorations seem to have in final position of soft tissues according to current evidence (Slagter et al., 2014). Instead, a submerged healing abutment was provided at the time of the DI surgery with the view of increasing the vertical dimension of soft tissues during the healing with the consequent positive impact this may have in final soft/hard tissues aesthetics (Salama et al., 2015).

Survival and success rate as primary outcomes: This clinical trial was designed to assess the impact of placing DI with flapless approach in soft and hard tissues due to the potential positive effect this may have in bone remodelling, flap vascularization/healing and DI aesthetics. Implant survival has been traditionally used as a primary outcome measurement because it provides long-term data on the predictability of OI. However, there are several limitations associated with this specific outcome (Needleman et al., 2012), such as:

i. The presence or absence of the implant in the patient's mouth per se may not be associated with the maintenance or re-establishment of the patient well-being (psychosocial characteristics and quality of life, absence of disease, function, aesthetics).

ii. Lack of consensus of how to define implant survival. Although well-defined criteria exist, not all studies use the same one, creating some limitations when comparing studies with different criteria.

iii. The reported high survival rates require large sample size and/or long-term follow-up for clinical research.

Despite of these limitations, it was decided to include this as one of the primary outcomes as it is one of the most reported in implant dentistry, creating a strong body of evidence to contrast the results of this study.

Success rate was also included in the present study. Conversely to DI survival that fundamentally reports whether a DI is in function in the mouth without any obvious problems, implant success goes a step further and takes into account (depending on the criteria used) other elements such as progressive bone loss, disease of peri-implant mucosa and, more recently, aesthetics and patient reported outcomes. Therefore, success rate seems somehow a more appropriate way to report DI outcomes. However, as pointed by Needleman et al. (2012), consensus has not been reached for "success", with several authors providing their own criteria (Albrektsson et al. (1986); Carr Wolfaardt & Garrett (2011); Misch et al. (2008)). Therefore, the lack of universally accepted success criteria makes the interpretation and comparison of the data between studies extremely difficult and constitutes a problem in the implant dentistry literature (Ong et al., 2008). Despite of the limitations outlined above, it was decided to use "Albrektsson Criteria" (Albrektsson et al., 1986) as it is one of the most widespread criteria used among studies (Needleman et al., 2012), with an additional component that considers aesthetics of DI surrounding mucosa and restoration (Cosyn et al, 2011). This was agreed because DI in the present study were placed in the anterior region, therefore final aesthetics were equally important as function for the treatment to be considered successful. To assess this aesthetic component, the "Pink Aesthetic Score (PES)" and "White Aesthetic Score (WES)" were used.

The use of PES/WES indexes for aesthetic evaluation. The use of PES/WES scores were preferred for this study as they are currently considered the most complete and objective indexes, demonstrating the highest repeatability among all objective aesthetic indexes (Tettamanti et al., 2016).

Assessment of buccal plate resorption after immediate DI placement. According to current evidence, there are not many studies that have been able to investigate this resorption process of the buccal plate. This is due to the limitations of traditional radiographic imaging to assess this structure three-dimensionally and the ethical issues that may arise from elevating a flap from a DI that is already osseointegrated and in function. Recent studies seemed to have overcome this problem by the use of newer cone beam computed tomography (CBCT) imaging at different time intervals (Benic et al. (2012); Kuchler et al.

(2015); Mazzocco et al. (2017)) due to its wider availability and less radiation used in modern CBCT machines. Due to the importance of the buccal wall plate thickness and the impact this may have in DI aesthetic in the short/long term, evaluation of this feature was included in our study.

The use of PROMs. As mentioned in the introduction chapter, PROMs are becoming increasingly more important. This was also highlighted in the VIII European Implant Workshop where one of the main conclusions was that patient's reported outcomes were under-reported and these should be included in future studies (Lang et al., 2012). This is the reason why these were included as one of our secondary outcomes. Specifically, a VAS and a patient questionnaire (de Bryn et al., 1997) were used to assess patients' satisfaction with final DI aesthetics and overall treatment outcome. However, some shortcomings were identified with these tools. Firstly, a questionnaire used to measure PROMs should have been designed and validated prior its application. For this, firstly the literature needs to be reviewed to confirm the lack of a tool to measure the desired outcome. If this is confirmed, the generation process can start by finding the theoretical base for the design of this new tool and trying to meet the following characteristics:

i. Acceptable. This is the extent to which an instrument is acceptable to patients. Indicators of acceptability include administration time, response rates, and levels of missing data.
ii. Feasible. This concerns the ease of administration and processing of an instrument. These are important considerations for staff and researchers who collect and process the information produced by patient-reported instruments.
iii. Interpretable, meaning the meaningfulness of scores produced by an instrument.
iv. Precise, concerning the number and accuracy of distinctions made by an instrument.
v. Reliable. This is whether an instrument is internally consistent or reproducible, and it assesses the extent to which an instrument is free from measurement error. It may be regarded as the proportion of a score that is signal rather than noise. As the measurement error of an instrument increases, so does the sample size required to obtain precise estimates of the effects of an intervention.
vi. Valid, meaning the extent to which an instrument measures what is intended.
vii. Responsive. This is related to the measurement of important changes in health and is therefore relevant when instruments are to be used in an evaluative context for the measurement of health outcomes.

Once a tool is designed keeping all characteristics in mind, an item generation process should commence for the design of the tool/questionnaire. This would lead to a pre-testing/pilot study where this tool would be used to collect feedback from a small cohort of patients such as acceptability, interpretability, etc... Once the tool has been refined further, some test should be performed to assess reliability and validity prior to its use in a large cohort of patients. Finally, this tool would be refined if needed and appraise by a panel of experts to confirm the adequacy of this tool to measure the intended outcome.

When looking at the existing literature, VAS has been validated to measure PROMs in dentistry, mainly for anxiety (Appukuttan, Vinayagavel & Tadepalli (2014); Facco et al. (2011)), but not for aesthetic outcomes to the extent our knowledge. Although the information that comes from such non-standardized questions and way of measuring may be valuable from an exploratory point of view, the validity and reliability of this approach may be questionable. As a result, it may be difficult, if not impossible to compare studies based on such questions.

The survey used to assess patients' satisfaction with treatment provided was based in a questionnaire developed by de Bruyn et al. (1997). However, neither this questionnaire nor the modifications introduced for this study were validated as a tool to measure the desired effect, therefore the limitations mentioned for the VAS also apply to this questionnaire. Based on this, our results regarding PROMs must be interpreted cautiously. The use of non-validated tools to measure PROMs in implant dentistry seems to be a common drawback in most of the studies reporting this type of outcomes. This was the conclusion reach by a systemic review conducted by De Bruyn, Raes, Matthys & Cosyn (2015) in which it was concluded that "an "ad hoc" approach is commonly employed using non-standardized questions and different scoring methods, which may compromise validity and reliability". At present, the only validated tools used for PROMs in implant dentistry are "Oral Health Impact Profile" (OHIP-49), "OHIP-14" developed by Slade & Spencer (1994) and 'Oral Health Related Quality of Life' (OHRQoL). All were developed to assess the impact of oral health on the overall well-being of individuals and include some questions relating to aesthetics aspects.

6.2 DISCUSSION OF RESULTS.

The failure rate for immediate/single implants (0%) was within the range reported in previous studies (Kuchler et al. (2015); Pjetursson et al. (2007); Prati et al. (2017); Tonetti et al. (2017)), therefore this study may support the fact that a flapless approach is a valid modality of treatment to handle complex aesthetic cases. However, when success rate was assessed, a noticeable discrepancy was noted favouring control group, although not statistically significant (flapped approach). Success rate ranged from 69.2% to 84.6% in the test group whereas this ranged from 84.6% to 92.3% in the control group. These figures seem to correlate with the success rate of immediate DI reported in several studies (Atieh et al. (2013); Chen et al. (2007); Cosyn et al. (2011); Covani et al. (2014), Esposito et al. (2015)), however, the main difference with the present study is that they all seem to have different success criteria, most of which used the one defined by Albretksson et al. (1986). This criterion takes into account successful osseointegration, lack of complications and bone loss (less than 0.2mm/year after loading) but this is somehow insufficient when assessing DI in the aesthetic region as there are other factors, such as soft tissues and final restoration, which would have a critical impact in the perception of success/failure of the treatment provided. That is the reason why PES/WES scores were included in our study to define success criteria. To exemplify the major impact this has had in our study and the impact this may have had in the success rates of other studies one should note that if PES/WES were not part of our success criterion, success rate would have been 100% for both groups, higher than reported in all

mentioned studies. This situation highlights the need to routinely report success rates (a large proportion of studies reviewed for the elaboration of this PhD only mentioned survival rates) as well as agreeing in a way to report success, ideally including soft tissue and final restoration elements. This was further corroborated in a systematic review on single implants in the anterior maxilla (den Hartog et al., 2008) where it was concluded that few reports included data on clinical parameters such as aesthetic or patient reported outcomes. To finalise the analysis of the success rate in this study, it is worthwhile noticing that most of the failures were noted in the WES scores. This has an important implication in the interpretation of the results as although control (flap) approach was more successful that test (flapless) approach, this does not seem to be due to a poorer healing of the soft tissues or PES scores but rather difficulties encountered at a later stage to restore the fixtures (lower WES scores). It may be hypothesised that blind placement of DI (flapless) is more technically demanding and therefore more prone to incorrect fixture placement. This may lead to more difficulties when restoring these DI with the consequent negative impact in final restoration aesthetics.

For the aesthetic assessment of the cases, PES/WES scores were used. A high intra-examiner correlation was noted for all groups and therefore examiners were deemed reliable, being orthodontists (0.88) the strongest. This seems in agreement with other studies (Furhauser et al. (2005); Gehrke, Lobert & Dhom (2008)) in which it was reported that the dental specialisation may have a significant impact on the intra- and inter-observer agreement of the pink aesthetic score, being orthodontists more critical and reproducible in assessing aesthetics. PES/WES test is considered an objective index demonstrating the highest repeatability among all objective aesthetic indices (Tettamanti et al., 2016) but is expected that the results vary with different examiners (den Hartog, Raghoebar, Stellingsma, Vissink & Meijer, 2011), even the same person re-evaluating a situation at a second- time point (Schropp & Isidor, 2008). The same was found in our study when the inter-examiner correlation was explored. No statistically significant difference was noted for PES/WES between groups. As mentioned before, not many studies seems to report PES/WES scores and most of studies reporting PES/WES in anterior region for immediate DI also provide immediate restoration (Cosyn et al. (2011); Esposito et al. (2015); Felice, Pistilli, Barausse, Trullenque-Eriksson & Esposito (2015); Nimwejen et al. (2018)). Overall, it seems that most of the studies providing immediate DI with immediate restoration report slightly better results than the ones reported in our trial. Most of the reported PES scores range between 11-13 (Cosyn et al. (2011); Esposito et al. (2015); Felice et al. (2015); Nimwejen et al. (2018)) although others report scores in the range of 8 to 11 (Cosyn et al. (2013); De Angelis et al. (2011)) at twelve months post-loading. It may be hypothesised that the use of an immediate restoration may have a greater impact in final aesthetic scores preventing the collapse of papilla and soft tissues than the choice of surgical technique for flap manipulation (flap vs. flapless). This is reinforced further by the results of mixed effect model for PES/WES as no association was found between WES and any of the covariates and no association was found between PES and “flapless approach” or “Distance DI - External Cortical Plate (mm) at 12 month”. This finding was rather unexpected as during the design of this study it was thought that a flapless approach may have led to less resorption/remodelling with the consequent positive impact in the PES scores. However, statistically significant association was found between “Total PES Score” and “Examiner Periodontist” and “Examiner Prosthodontist group” meaning that these groups gave better result for PES scores than “Examiner GDPs”

and “Examiner Orthodontists”. Alternatively, this may be also interpreted as Orthodontists and GDPs were more critical evaluating soft tissues than the other groups. This seems in agreement with other studies (Furhauser et al. (2005); Gehrke et al. (2008)), in which it was reported that the dental specialisation may have a significant impact on the inter-observer agreement of the pink aesthetic score, being orthodontists more critical in assessing aesthetics. Of particular importance is the overall aesthetic outcome combining the results of the PES and WES. As such, between 7.7% to 30.7% in both groups (depending on the examiner) showed perfection (PES equal or above 12 and WES equal or above 9) which is quite modest, yet in agreement with the knowledge on single implant treatment (7–35%) (Belser et al. (2009); Buser et al. (2009); Cosyn, Eghbali, De Bruyn, Dierens & De Rouck (2012); Raes, Cosyn, Crommelinck, Coessens & De Bruyn (2011)). Similarly, 15.4% to 30.8% of our cases could be considered aesthetic failures (PES<8 and/or WES<6) which also falls within the range of what has been published (5–34%) (Belser et al. (2009); Buser et al. (2009); Cosyn et al. (2012); Meijndert, Meijer, Stellingsma, Stegenga & Raghoebar (2007); Raes et al. (2011)). Optimal aesthetics seem difficult to achieve and failures are quite prevalent although patients had been selected carefully and treated by an experienced clinician. Therefore, patients should be warned about these aesthetic challenges before embarking with treatment.

Regarding radiographic outcomes, there is not much data published about buccal plate thickness at 12-month post-loading due to the ethical issues that may arise to elevate a flap at that stage. This is an important aspect to consider as loss of buccal plate may lead to soft tissue recession with the associated aesthetic deficiency. Therefore, being able to minimise this resorption/remodelling and predict how much resorption may be expected in time would be crucial information that may change the way aesthetic implant cases may be handled. The approach taken in some studies to assess resorption rate during a period of time has been to either follow the same protocol used in this study (measuring distance between DI surface and external aspect of buccal plate at the time of fixture placement and to see how this compares with a CBCT examination provided at a later stage (Benic et al. (2012); Kuchler et al. (2015)) or taking a CBCT the day of the immediate fixture placement and another one at the desired time interval (Mazzocco et al., 2017). Most of the studies performed in human subjects report about buccal plate thickness changes at different time intervals such as 4 months (Botticelli et al. 2004), 6 months (Mazzocco et al., 2017), 5 years (Benic et al., 2012) or 7 years (Kuchler et al., 2015), therefore it is rather difficult to assess if resorption/remodelling reported in this study is above/below expected. The difference in buccal plate thickness examined at 12-month CBCT compared to baseline intraoperatively measurements was of 0.72mm in control group and 0.92 in test group. These results seem to indicate that although there was not a statistically significant difference between the groups it seemed that there was less buccal bone resorption in the control group (flap). According to current knowledge in bone remodelling, the fact that a flap was not raised and more periosteum was left intact in the test group, it would have been expected that less bone remodelling/resorption would occur in this group (Blanco et al., 2008). However, findings in this study pointed that this did not make any difference. It could be hypothesised that some difficulties associated with access/visibility may have been experienced during GBR procedures in the flapless group and therefore having a negative impact in the preservation of the buccal plate. Finally, as it will explained later in this paragraph, the methodology used to assess bone resorption was not ideal due to the differences in the methods used to

evaluate the buccal plate thickness at the two time points. Therefore, these findings should be interpreted cautiously.

Regarding patients' reported outcomes, the overall patients' satisfaction with final aesthetics was very high (>85%in the VAS scale for both groups at 12-month post-loading review). This seems to be in agreement with one of the latest systematic reviews looking at VAS reported outcomes for DI supported prosthesis (Wittneben, Wismeijer, Bragger, Joda & Abou-Ayash, 2018) in which a mean "VAS for mucosa" of 84.7 (median: 86.7; min–max: 73.0–92.0) and mean "VAS for restoration" of 88.9 (median: 90.3; min–max: 80.0–94.0) was reported in the included studies. No significant differences were observed comparing test and control subjects at any of the analysed intervals. Based on this it seems reasonable to state that both treatment modalities were equally successful for patients from an aesthetic point of view. Patient's satisfaction survey showed that all patients were satisfied with treatment provided and it may be argued that the success rate quoted in this study according to clinicians' perception may not necessarily match the one based on PROMs. Similar findings were reported by Cosyn et al. (2013); Esposito, Grusovin & Worthington (2009) and Meijndert et al. (2007) in the sense that patients were less critical than clinicians when judging aesthetics. In the latest study (Esposito et al., 2009), four standardized clinical preoperative and postoperative pictures placed in random order were shown to 30 patients treated with dental implants, on two separate occasions, to subjectively evaluate the aesthetic changes using both a graded scale and a visual analogue scale (VAS). In general, agreement was moderate to substantial among patients but only fair among clinicians and agreement between patients and clinicians was poor. This highlights the need of taking into consideration PROMs in the definition of success and should be included in future studies.

Based on all exposed during this study, I believe the strong features of this PhD could be as summarised below:

- Design. Randomised controlled trials are currently considered the gold standard due to random allocation of subjects to different treatment groups and therefore eliminating/reducing certain biases such as selection and allocation bias.

- Blinding. Participants, evaluators, and data analyst were blinded. Operators could not be blinded but treatment assignment was concealed until completion of tooth extraction and final assessment of the feasibility of immediate implant placement.

- Inclusion of accepted aesthetic indexes (PES/WES) to objectively assess DI aesthetics as well as providing a better estimation of success rate by adding an aesthetic component.

- The use PROMs. This has been under-reported in past studies (den Hartog et al., 2008) and it is quite important to include these in future studies due to the increasing importance of patient's perceptions about treatment provided.

- CBCT examination at 12 months. Newer CBCT machines use less radiation to perform the required radiographic examination and capture more accurately the anatomical features of the structure under investigation. This has allowed the routine use of this

technology with the consequent benefit this has had in treatment planning and outcome evaluation. In this study, the use of this technology has allowed us to assess the thickness of the buccal cortical plate 12 months after DI placement as well as stablishing comparisons between two different treatment modalities. The thickness of the buccal plate is a very important structure as it is directly related with mucogingival levels and potential aesthetic outcomes. This examination could not have been achieved with traditional imaging and there are not many studies reporting about this.

The limitations of this PhD study are:

- Power. Due to time limitations for the elaboration of this PhD, results were based in 14 subjects per group rather than 20 as originally plan. Even with the planned sample size it may have been argued that a higher sample would have provided more meaningful results. Therefore, there is a chance that a type-II error occurred during the statistical analysis. However, the sample used for the elaboration of this PhD (28 patients) is a standard figure when compared with most of the current published studies evaluating DI treatment.

- Methods used to evaluate cortical plate thickness at 0mm. Ideally, the same method/tool should be used to measure a clinical outcome. The fact that intraoperative measures and CBCT examination were used at different times to measure buccal plate thickness could considered a shortcoming in this study as ideally statistical analyses should not be performed for the same outcome measured in two different ways. Intraoperative measures were not performed at 12-month review for obvious ethical reasons but having performed a CBCT at DI placement and then comparing it with CBCT at 12 months would have provided a more accurate way to measure this variable.

- Study follow up. Most of studies investigating around the same topic provide outcomes at 12 months. However, longer follow-up periods would be desirable to ascertain the long-term performance and stability of investigated treatment modalities.

- The use of non-validated tools for patient reported outcomes. As mentioned earlier in this paragraph, this approach is commonly employed, which may compromise validity and reliability of these results.

VII. CONCLUSIONS

Within the limits of the present study, it could be concluded that:

1. Immediate DI placed in the anterior/premolar region of the maxilla using a flapless vs. flap approach with simultaneous soft/hard tissue grafting had a similar survival rate (100%).

2. Immediate DI placed in the anterior/premolar region of the maxilla with simultaneous soft/hard tissue grafting using a flapless approach had a lower success rate (69.2% to 84.6%) vs. a flap approach (84.6% to 92.3%). However, these differences were not statistically significant.

3. Immediate DI placed in the anterior/premolar region of the maxilla using a flapless vs. flap approach with simultaneous soft/hard tissue grafting had a similar mean buccal plate resorption/remodelling at 12 months post-loading.

4. Immediate DI placed in the anterior/premolar region of the maxilla using a flapless vs. flap approach with simultaneous soft/hard tissue grafting had a similar mean PES/WES scores at 12 months post-loading.

5. Immediate DI placed in the anterior/premolar region of the maxilla using a flapless vs. flap approach with simultaneous soft/hard tissue grafting lead to similar patients' satisfaction outcomes and perception of final aesthetic result.

VIII. REFERENCES

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IX. EXTENDED SUMMARY IN SPANISH

EXTENDED SUMMARY IN SPANISH:

Introducción:

El implante dental inmediato a la exodoncia es una alternativa predecible en la rehabilitación de un diente natural perdido (Belser, Schmid, Higginbottom y Buser 2004), constituyéndose en un tratamiento estándar como terapia para sustituir dientes con una función y apariencia similar a la de los dientes naturales (Andersson et al., 1995). Múltiples estudios longitudinales a más de 5 años han demostrado la eficacia y vida útil clínica de implantes osteointegrados múltiples (Romeo, Chiapasco, Ghisolfi y Vogel (2002); Scheller et al.,(1998)) Igualmente, se han demostrado altas tasas de éxito para implantes unitarios, semejantes a las de prótesis implanto soportadas sobre más de un implante (Andersen, Haanaes y Knutsen (2002); Chen, Wilson y Hammerle (2004); Gallucci, Hamilton, Zhou, Buser y Chen (2018); Gotfredsen (2004); Palmer, Smith, Palmer, Floyd (1997); Pjetursson et al., (2007)). Por tanto, hoy en día podemos afirmar que los implantes osteointegrados unitarios y su carga mediante prótesis dentales tienen un elevado porcentaje de éxito a medio y largo plazo (Gallucci et al., (2018); Wagenberg y Froum (2006)).

Actualmente, el problema principal para los pacientes y los investigadores se ha trasladado al aspecto estético del uso de estos elementos (Buser, Martin y Belser (2004); Higginbottom, Belser, Jones y Keith (2004); Jemt, (1997)) más aún, un implante es considerado exitoso, sólo si, después de su restauración protésica, logra patrones que son aceptados por el paciente. La ubicación de los implantes en zonas que permitan un resultado armónico con el resto del sistema estomatognático fue el principio de estas preocupaciones (Garber (1996); Palmer et al., (1997); Phillips y Kois (1998)). Luego, se dirigió a conseguir tejidos periodontales, similares en apariencia a los que se presentan en los dientes naturales (Al-Harbi, (2005); Artzi, Tal, Moses y Kozlovsky (1993); Carrion y Barbosa, (2005); Garber, (1996)). El objetivo de las nuevas técnicas implantológicas debe ser simplificar la fase quirúrgica y protésica acortando los tiempos finales del tratamiento. La inserción de implantes oseointegrados en alvéolos tras una exodoncia es una de las técnicas que se incluyen dentro de dichos procedimientos (Oh, Shotwell, Billy, Byun y Wang, 2007). Pese a que los implantes inmediatos a la exodoncia ha demostrado ser una técnica óptima para mantener el volumen óseo y el nivel del margen gingival, en estudios experimentales en modelo animal se ha observado que la colocación de implantes inmediatos no sirve para prevenir el remodelado que ocurre en las paredes de un alvéolo postexodoncia y la consecuente recesión gingival (Araújo y Lindhe (2009); Araujo et al., (2005)).

La introducción de implantes en alvéolos inmediatos a la exodoncia puede llevarse a cabo con el levantamiento de un colgajo mucoperióstico a espesor total o sin la realización de éste. Clásicamente la cirugía implantológica se ha basado en la realización de colgajos más o menos amplios que permitían la visión directa del tejido óseo. No obstante, el intento por minimizar el dolor y conseguir el mantenimiento de la morfología del tejido duro y blando ha llevado al desarrollo de procedimientos quirúrgicos en los cuales se obvia este paso de la cirugía (Pfeifer, 1965). De esta forma los implantes se colocan a través del alveolo resultante tras la exodoncia sin realizar un colgajo mucoperióstico obteniendo una serie de ventajas considerables frente a la técnica con colgajo: máxima conservación de los tejidos, disminución

del dolor postoperatorio y simplificación de los tiempos quirúrgicos y prostodóncicos (Becker, Goldstein, Becker y Sennerby, 2005). La cirugía de implantes inmediatos sin colgajo se ha sugerido como un procedimiento óptimo para la conservación de los tejidos blandos y la obtención de la máxima estética ya que los lugares más habituales para la colocación de implantes inmediatos son la zona anterior (caninos e incisivos) y la zona de premolares del maxilar superior y mandíbula (Oh, Shotwell, Billy y Wang, 2006). Estos mejores resultados estéticos son debidos a la menor pérdida de tejido óseo crestal en las situaciones en las que se recurre a procedimientos sin colgajo frente a cirugías con colgajo (Villa y Rangert, 2007). De hecho, se puede afirmar que el objetivo principal de este tipo de técnica quirúrgica es preservar la morfología protegiendo al máximo los tejidos blandos y duros preexistentes (Zeren, 2006).

Basándonos en lo expuesto anteriormente, el objetivo de esta tesis es comparar la tasa de supervivencia/éxito, resultados estéticos y reabsorción de la tabla vestibular en implantes inmediatos postexodoncia (Biomimetic OCEAN, Avinent®) mediante la elevación de un colgajo mucoperióstico vs. no colgajo. Para la evaluación de dichos parámetros se utilizaron datos clínicos y radiográficos, índices estéticos (PES/WES) e información relacionada con el paciente al año poscarga.

Objetivos de la investigación:

- ***Objetivo primario*:** Comparar la tasa de supervivencia y éxito de implantes inmediatos postexodoncia en la zona anterior y premolar del maxilar elevando un colgajo mucoperióstico en el grupo control y no elevando colgajo en el grupo test. En ambos grupos se realizaron injertos de tejido duro y blando de manera simultánea durante la colocación del implante.

- ***Objetivos secundarios:***
  i. Comparar la estética de los tejidos blandos y de la restauración implantosoportada en implantes inmediatos postexodoncia en la zona anterior y premolar del maxilar elevando un colgajo mucoperióstico en el grupo control y no elevando colgajo en el grupo test. En ambos grupos se realizaron injertos de tejido duro y blando de manera simultánea durante la colocación del implante.
  ii. Comparar la reabsorción/remodelado de la cortical ósea vestibular en implantes inmediatos postexodoncia en la zona anterior y premolar del maxilar elevando un colgajo mucoperióstico en el grupo control y no elevando colgajo en el grupo test. En ambos grupos se realizaron injertos de tejido duro y blando de manera simultánea durante la colocación del implante.
  iii. Comparar la satisfacción del paciente con los procedimientos, así como con la estética resultante en implantes inmediatos postexodoncia en la zona anterior y premolar del maxilar elevando un colgajo mucoperióstico en el grupo control y no elevando colgajo en el grupo test. En ambos grupos se realizaron injertos de tejido duro y blando de manera simultánea durante la colocación del implante.

Materiales y métodos:

Este estudio clínico fue randomizado, controlado y con grupos paralelos para comparar datos clínicos y radiográficos, índices estéticos (PES/WES) e información relacionada con el paciente al año poscarga en implantes inmediatos realizados con colgajo mucoperióstico vs. no colgajo. En todos los casos, la discrepancia/espacio entre el implante y la pared interna del alveolo se rellenó con una mezcla de injerto autólogo con xenoinjerto de origen bovino (Gen-Os, Osteógenos s.r.l.) todo ello cubierto con una membrana de colágeno reabsorbible de origen animal (Evolution, Osteógenos, s.r.l). Además, todos los casos recibieron un injerto de tejido conectivo autógeno para aumentar el grosor y volumen de la encía en la zona del implante.

- **Criterio de inclusión y exclusión:**

Participaron en el estudio sujetos adultos (mayores de 18 años) a los que había que realizar una extracción dental en la zona anterior o premolar del maxilar superior como consecuencia de trauma dental, enfermedad periodontal, patología pulpar y/o imposibilidad de restaurar la pieza dental. Sin embargo, aquellos sujetos que presentaron alguna de las siguientes condiciones fueron excluidos del estudio:

i. Enfermedades sistémicas significativas como quimio/radioterapia en la región de la cara/cuello como resultado de enfermedades tumorales, pacientes diabéticos no controlados o pacientes en tratamiento con bifosfonatos.
ii. Fumadores.
iii. Presencia de enfermedad periodontal activa.
iv. Altos niveles de placa bacteriana (Índice de placa por encima de 25%).
v. Presencia de enfermedad apical en la pieza dental a extraer.
vi. Ausencia de suficiente volumen óseo para la inserción del implante inmediato postexodoncia.
vii. Ausencia de suficiente espacio prostético para la restauración el implante.
viii. Imposibilidad de atender a las citas necesarias para completar el estudio.

- **Randomización, enmascaramiento y evaluación de resultados:**

Acorde con el criterio de inclusión e inclusión, una muestra de 40 casos de estudio (20 grupo control y 20 grupo test) fueron reclutados. La asignación al grupo control y test fue realizada mediante un proceso de aleatorización en bloques balanceados con la ayuda de una tabla de números aleatorizados generada por ordenador. Los grupos de tratamiento fueron enmascarados mediante el sistema de sobres opacos que fueron entregados al cirujano una vez que este extrajo la pieza dental y verificó la posibilidad de colocar un implante inmediato. Los grupos de tratamiento fueron ciegos para evaluadores, pacientes y estadístico.

- **Intervenciones del estudio:**

Todos los sujetos candidatos recibieron un examen periodontal inicial, incluyendo profundidad de sondaje, recesión, nivel de inserción clínica y sangrado al sondaje en todos los dientes presentes, excluyendo terceros molares, en seis localizaciones por diente. Tras establecer el diagnóstico periodontal, todos los sujetos que cumplieron con los criterios de inclusión/exclusión fueron invitados a participar en el estudio hasta alcanzar los tamaños muestrales preestablecidos.

Implantes Biomimetic OCEAN (Avinent ® Implant System S.L.) fueron insertados de manera inmediata tras la exodoncia, realizando colgajo mucoperióstico en el grupo de control y sin la elevación de colgajo en el grupo test. En todos los casos se realizó regeneración de tejidos blandos mediante injerto de tejido conectivo y regeneración ósea del gap residual entre el implante y el alvéolo mediante hueso autólogo, biomaterial (Gen-Os, Osteógenos s.r.l.) y membrana de colágeno (Evolution, Osteógenos, s.r.l.).

i. Evaluación de tejidos duros (tejido óseo crestal).

Una vez el implante fue insertado de manera inmediata, las siguientes medidas intraoperatorias fueron registradas en la historia del paciente:

- Distancia entre la superficie del implante a nivel de la plataforma y la zona interna de la cortical ósea vestibular.
- Distancia entre la superficie del implante a nivel de la plataforma y la zona externa de la cortical ósea vestibular.
- Distancia entre el hombro del implante y la zona más apical del defecto vestibular entre el Implante y la zona interna de la cortical ósea vestibular.

Finalmente, se realizó un examen radiográfico (CBCT) a los 12 meses de carga del implante para evaluar el grosor de la cortical ósea vestibular a 0, 3 y 6 mm apical del hombro del implante.

ii. Evaluación de tejidos blandos. "Pink aesthetic Score (PES)".

La evaluación de tejidos blandos fue realizada mediante el test Pink Aesthetic Score (PES) desarrollado por Fürhauser en 2005 para obtener una medición estética objetiva (Fürhauser et al., 2005). El autor afirmó que el resultado estético conseguido se debía principalmente por el logro de ciertas cualidades gingivales, por lo tanto, diseñó un test que está compuesto por preguntas en relación a 7 variables; a cada variable se le asignó una puntuación de 0, 1 ó 2. Una puntuación de 0 indicaba el peor resultado y una puntuación de 2 indicaba el mejor resultado, por lo tanto, la puntuación más alta posible que se puede lograr son 14 puntos, reflejando plena conformidad entre el tejido blando del implante evaluado y la del diente de referencia. Con la excepción de la formación de papila, la evaluación se realiza visualmente comparando los tejidos blandos de la corona sobre el implante con el diente de

referencia (con el diente contralateral en la zona incisiva-canina y en el diente adyacente en la zona de premolares). Estas variables fueron evaluadas por dentistas agrupados según su especialidad. Las conclusiones a las que llegaron en este estudio fueron que los puntajes de la estética rosa evalúan reproduciblemente el tejido blando peri-implantario alrededor de implantes unitarios.

iii. Evaluación de la estética blanca." White Aesthetic Score (WES)".

En el año 2009, Belser modificó el test anteriormente descrito reduciendo el número de variables del PES a 5 y además añade el concepto de WES (puntuación de la estética blanca), que además de tener en cuenta los tejidos blandos peri-implantarios, también valora la restauración protésica. La puntuación máxima que se puede obtener es de 10 para PES y WES. Por lo tanto, la combinación más alta posible PES / WES es de 20 (Belser et al., 2009).

iv. Variables del estudio.

Como variable primaria del estudio se consideró la tasa de supervivencia y éxito del implante. Con respecto al éxito del implante, utilizamos los criterios descritos por Albretksson (Albrektsson, Zarb, Worthington y Eriksson, 1986) añadiendo ciertos valores de los índices estéticos. Para ello, un implante se consideró exitoso siempre y cuando el valor PES fuese mayor de 7 y el WES mayor de 5 (Cosyn et al., 2011).

Las siguientes variables se consideraron secundarias para el estudio.

- Valores PES/WES a los 12 meses.
- Grosor radiográfico de la tabla vestibular a los 12 meses.
- Respuesta del paciente mediante escala analógica y cuestionario al finalizar el tratamiento y a los 12 meses.

Resultados:

40 casos fueron randomizados, de los cuales 28 se incluyeron para el desarrollo de la tesis. Ningún implante fracasó durante la duración de estudio. La tasa de éxito varió entre 62.9%-84.6% en el grupo test y entre 84.6%-92.3% en el grupo control acorde con los criterios expuestos anteriormente. Sin embargo, estas diferencias no fueron estadísticamente significativas. Con respecto a la reabsorción/remodelado de la cortical ósea vestibular, no se hallaron diferencias significativas entre el grupo control (0.72 +/-0.22) y el grupo de estudio (0.92+/-0.31) al año post-carga. Tras el análisis de la estética al año post-carga, no se detectaron diferencias significativas en el PES (10.54 control vs. 10.80 test) o WES (6.97 control vs. 6.95 test). Cuando la respuesta de los pacientes al tratamiento control y test fue evaluada mediante una escala visual analógica (VAS) y un cuestionario, la mayoría de los

sujetos reportó un alto índice de satisfacción con el tratamiento recibido (por encima del 85% en ambos grupos)-sin observar diferencias significativas entre los grupos de estudio.

Para finalizar, se realizó un análisis de modelo para efectos mixtos para valorar la posible asociación de los resultados obtenidos con PES y WES con las variables "grupo que hizo la observación" y "grosor de cortical ósea vestibular". La única asociación estadísticamente significativa que se encontró fue entre PES y grupo de observación. Estos grupos (periodoncista y ortodoncista) dieron un mejor resultado PES que fue estadísticamente significativo comparado con los resultados dados por el grupo referencia (dentistas generalistas).

Conclusiones:

1 Los implantes inmediatos en la zona anterior/premolar de maxilar sin elevación de colgajo mucoperióstico e injerto simultaneo de tejido duro y blando presentaron una tasa similar de supervivencia a los implantes inmediatos insertados con elevación de colgajo e injerto simultaneo de tejido duro y blando.

2 Los implantes inmediatos en la zona anterior/premolar de maxilar sin elevación de colgajo mucoperióstico e injerto simultaneo de tejido duro y blando presentaron una tasa inferior de éxito, aunque no estadísticamente significativa, comparados con los implantes inmediatos insertados con elevación de colgajo e injerto simultaneo de tejido duro y blando.

3 Los implantes inmediatos en la zona anterior/premolar de maxilar sin elevación de colgajo mucoperióstico e injerto simultaneo de tejido duro y blando no presentaron una diferencia significativa en la media de la reabsorción de la cortical vestibular a los implantes inmediatos insertados con elevación de colgajo e injerto simultaneo de tejido duro y blando.

4 Los implantes inmediatos en la zona anterior/premolar de maxilar sin elevación de colgajo mucoperióstico e injerto simultaneo de tejido duro y blando no presentaron una diferencia significativa en la media de los valores PES/WES a los 12 meses poscarga a los implantes inmediatos insertados con elevación de colgajo e injerto simultaneo de tejido duro y blando.

5 Los implantes inmediatos en la zona anterior/premolar de maxilar sin elevación de colgajo mucoperióstico e injerto simultaneo de tejido duro y blando no presentaron una diferencia significativa en la satisfacción del paciente y percepción estética a los 12 meses poscarga a los implantes inmediatos insertados con elevación de colgajo e injerto simultaneo de tejido duro y blando.

X. ANNEXES

9.1 Ethical approval.

UNIVERSIDAD DE MURCIA | Vicerrectorado de Investigación

CEI Comisión de Ética de Investigación

CAMPUS MARE NOSTRUM

INFORME DE LA COMISIÓN DE ÉTICA DE INVESTIGACIÓN DE LA UNIVERSIDAD DE MURCIA

Jaime Peris Riera, Catedrático de Universidad y Secretario de la Comisión de Ética de Investigación de la Universidad de Murcia

CERTIFICA:

Que D. Guillermo Pardo Zamora ha presentado el proyecto de investigación titulado *"Valoración del remodelado del tejido óseo y gingival en implantes insertados en alveolos post-exodoncia con y sin colgajo mucoperióstico en zona estética. Estudio clínico y radiológico prospectivo a 1 año"*, a la Comisión de Ética de Investigación de la Universidad de Murcia.

Que dicha Comisión analizó toda la documentación presentada y por unanimidad, se emite INFORME FAVORABLE, desde el punto de vista ético de la investigación.

Y para que conste y tenga los efectos que correspondan, firmo esta certificación, con el visto bueno del Presidente de la Comisión

Vº Bº
EL PRESIDENTE DE LA COMISIÓN
DE ÉTICA DE INVESTIGACIÓN DE LA
UNIVERSIDAD DE MURCIA

Fdo.: Antonio Juan García Fernández

ID: 1738/2017

9.2 Patient's information sheet.

UNIVERSIDAD DE MURCIA

FACULTAD DE ODONTOLOGÍA

CLÍNICA ODONTOLÓGICA INTEGRADA DE ADULTOS

INFORMACIÓN Y DECLARACIÓN ESCRITA DE CONSENTIMIENTO PARA LA PARTICIPACIÓN EN EL ENSAYO CLÍNICO

Estimado Sr. o Sra.:

Le invitamos a participar en un estudio de investigación sobre la valoración del remodelado del tejido óseo y gingival en implantes insertados en alveolos post-exodoncia con y sin colgajo mucoperióstico en zona estética. Estudio clínico y radiológico prospectivo a 1 año"

Lea detenidamente este formulario

Pregunte si no entiende algo o tiene alguna duda

INFORMACIÓN DEL ESTUDIO

1. OBJETIVOS DEL ESTUDIO

El objetivo del presente estudio es la evaluación clínica, radiológica y estética de implantes Avinent Ocean insertados inmediatos a la exodoncia y con regeneración de tejidos simultánea tras 12 meses de carga.

A usted, como participante del estudio, se le realizarán las mediciones pertinentes en los intervalos de tiempo estipulados. A título informativo, es importante que usted sepa que los materiales utilizados que van a ser evaluados en el presente estudio están aprobados por la CEE, comercializados y disponibles en el mercado.

2. PARTICIPANTES EN EL ESTUDIO

Podrán participar en el estudio todos aquellos pacientes que cumplan con las siguientes características:

Aceptar participar en el estudio de forma voluntaria.

Tener más de 18 años.

Tener que exodonciar un solo diente entre el segundo premolar superior izquierdo y el segundo premolar derecho (ambos incluídos) cuyos dientes adyacentes sean dientes naturales.

Antecedente médicos y odontológicos que permitan la colocación de implantes

No fumadores o fumadores de menos de 10 cigarrillos/día

Higiene oral adecuada y motivación para su mantenimiento.

3. CARÁCTER VOLUNTARIO DE LA PARTICIPACIÓN

Su participación en el presente estudio es absolutamente libre y voluntaria, por lo que usted puede negarse a participar. De igual modo, si decide participar en el estudio, podrá en todo momento revocar su decisión y abandonar el estudio. En ninguno de los dos casos anteriores se verá perjudicado su posterior tratamiento.

Del mismo modo, su participación también podrá ser interrumpida si el facultativo responsable así lo decide en el interés de su salud o por uno de los siguientes supuestos: porque no sea posible llevar a cabo el procedimiento requerido según el protocolo del estudio o bien porque no siga usted las instrucciones del protocolo. En ese caso, se le informará sobre métodos de tratamiento alternativos.

4. DATOS DE LOS INVESTIGADORES

Ante cualquier duda o renuncia que pueda surgir en relación con su participación en la presente investigación, pueden dirigirse a la persona responsable de la misma, cuyos datos son los siguientes:

Nombre: Guillermo Pardo Zamora

Cargo: Profesor ayudante doctor-responsable de la investigación.

Dirección de contacto: C/Huerto Pomares, nº 4, 30005, Murcia.

Correo electrónico: gparza@um.es **Teléfono de contacto:** 606064848

5. USO CONFIDENCIAL DE LOS DATOS

Los datos personales serán protegidos e incluidos en un fichero que estará sometido a y con las garantías de la ley 15/1999 de 13 de diciembre de protección de datos personales.

6. DESARROLLO DEL ESTUDIO

Para participar en el estudio es imprescindible acudir en varias ocasiones a la Facultad de Odontología, ya que para confeccionar un diente sobre un implante se necesitan varias citas *per sé*, y además debido a que el seguimiento del resultado obtenido está estipulado a 1 año.

A continuación se detallan las diferentes visitas que contempla el estudio:

VISITA 1. En primer lugar se realizará la historia clínica y a continuación una evaluación de su estado bucal para determinar si usted cumple con los criterios de inclusión para poder participar en el estudio. En caso se que así fuera, se le harán los siguientes procedimientos:

-Medición de las variables clínicas. Se le realizarán diferentes mediciones clínicas rutinarias en la exploración dental y de carácter no invasivo e indoloras.

-Fotografías intraorales.

-Radiografías convencionales en el diagnóstico implantológico para la evaluación del hueso y un escáner radiológico (CBCT).

VISITA 2. En la segunda visita se procederá a la exodoncia del diente no restaurable y a la colocación de un implante unitario (Avinent Ocean) siguiendo los procedimientos rutinarios de colocación de implantes. Una vez colocado el implante, se colocará un pilar de cicatrización, se regenerarán los tejidos y se suturará con puntos simples. Para el control del dolor y de la infección se recetarán analgésicos y antibióticos habituales para el tratamiento con implantes. Como parte perteneciente a la realización del estudio se realizarán las siguientes mediciones:

-Determinación del grosor de la encía

-Medición de las dimensiones del hueso con un calibre.

-Radiografía intraoral postoperatoria

-Fotografías postoperatorias

VISITA 3. A las 2 semanas de la colocación del implante se retirarán las suturas y se reforzarán las instrucciones de higiene oral dadas al comienzo del estudio. Como parte perteneciente a la realización del estudio se realizarán las siguientes mediciones:

-Fotografías intraorales.

-Registro del grado de higiene oral mantenido.

-Evaluación de las mediciones clínicas (idem visita 1).

-Registro de posibles reacciones adversas.

VISITA 4. A las 2 semanas de la visita anterior, como parte perteneciente a la realización del estudio se realizará una revisión del estado de los tejidos cicatrizados y de la higiene oral.

VISITA 5. Entre las semanas 6 y 8 se realizará la confección de una corona provisional para moldear y estabilizar los tejidos blandos durante 1 a 3 meses. Esta fase puede requiere varias visitas (número individualizado según se requiera en cada paciente) para confeccionar la corona, tal y como se realiza normalmente para poder rehabilitar un implante.

VISITA 6. Una vez moldeados los tejidos blandos con el provisional, confeccionaremos la corona definitiva sobre el implante. Esta fase puede requiere varias visitas (número individualizado según se requiera en cada paciente) para confeccionar la corona, tal y como se realiza normalmente para poder rehabilitar un implante.

VISITA 7. A las 12 semanas de la colocación del implante la restauración final deberá estar finalizada y colocada en boca y como parte perteneciente a la realización del estudio se realizarán las siguientes mediciones:

-Fotografías intraorales

-Radiografía intraoral de control y a su vez objeto de mediciones radiológicas.

-Registro de posibles efectos adversos.

VISITAS 8. A los 6 meses de haber colocado la corona, registraremos las variables clínicas y radiológicas previamente descritas, así como la toma de fotografías intraorales.

VISITAS 9. A los 12 meses de haber colocado la corona, registraremos las variables clínicas y radiológicas previamente descritas, así como la toma de fotografías intraorales y un escáner radiológico (CBCT).

9.3 Informed consent.

UNIVERSIDAD DE MURCIA

FACULTAD DE ODONTOLOGÍA

CLÍNICA ODONTOLÓGICA INTEGRADA DE ADULTOS

FORMULARIO DE CONSENTIMIENTO INFORMADO

Nombre: …….

DNI: ……

Dirección: ……..

Teléfono de contacto: …….

DECLARO:

-Que los facultativos de la Facultad de Odontología de la Universidad de Murcia han solicitado mi colaboración para participar en un estudio en el que van a evaluar el resultado estético de implantes Avinent Ocean insertados inmediatos a la exodoncia y con regeneración de tejidos simultánea tras 12 meses.

-Conozco la justificación y los objetivos del proyecto, que son la evaluación clínica, radiológica y estética de implantes inmediatos a la exodoncia.

-Ante la pérdida de un diente he decidido restaurarlo colocando un implante dental y previamente se me han explicado las diferentes opciones de tratamiento alternativas.

-Sé que la colocación de un implante inmediato a la exodoncia consiste en realizar la exodoncia del diente no restaurable y colocar el implante dentro del hueso, y que debo esperar 3 meses antes de realizar la prótesis para permitir la cicatrización del hueso.

-Acepto la realización de las pruebas diagnósticas requeridas, incluyendo los estudios clínicos, radiográficos y fotográficos previamente descritos en el apartado anterior.

-He sido informado sobre los posibles riesgos de la anestesia local, necesaria para la intervención quirúrgica.

-Se me ha explicado que existen ciertos riesgos potenciales de toda intervención quirúrgica bucal, siendo lo habitual: inflamación, hematomas y molestias postoperatorias, con posibilidad de sangrado durante los primeros días. Asimismo, con menor frecuencia y debido a las características individuales de cada persona podrían presentarse: infección, apertura de la herida, aspiración o deglución de instrumentos, fractura de componentes. De manera excepcional y según el área a intervenir, puede producirse: lesiones en dientes vecinos, labios y encía, que podrían llegar a ser permanentes como la sinusitis.

-Sé que aunque la técnica se realice correctamente, existe la posibilidad de fracaso del implante, siendo necesaria una nueva intervención. Por ello, no existen garantías absolutas sobre el resultado exacto del tratamiento realizado, a pesar de que el riesgo de fracaso es bajo.

-Si surgiese cualquier situación inesperada, el facultativo podrá realizar cualquier maniobra o procedimiento distinto del planificado que a su juicio considerase oportuno.

-Se me ha explicado que para la realización del estudio, así como la colocación habitual de implantes, es imprescindible mantener una higiene oral adecuada.

-Dado que acepto participar en el estudio, me comprometo a acudir a las visitas planificadas de las que he sido informado por escrito y verbalmente por el facultativo.

-He comprendido con claridad las explicaciones facilitadas por los facultativos, y he podido plantear todas las dudas y observaciones que he considerado necesarias.

-En cualquier momento y sin necesidad de dar ninguna explicación, puedo revocar el consentimiento que ahora presto.

Por todo lo anterior expuesto, manifiesto que estoy satisfecho con la información recibida y doy mi consentimiento para participar en el estudio.

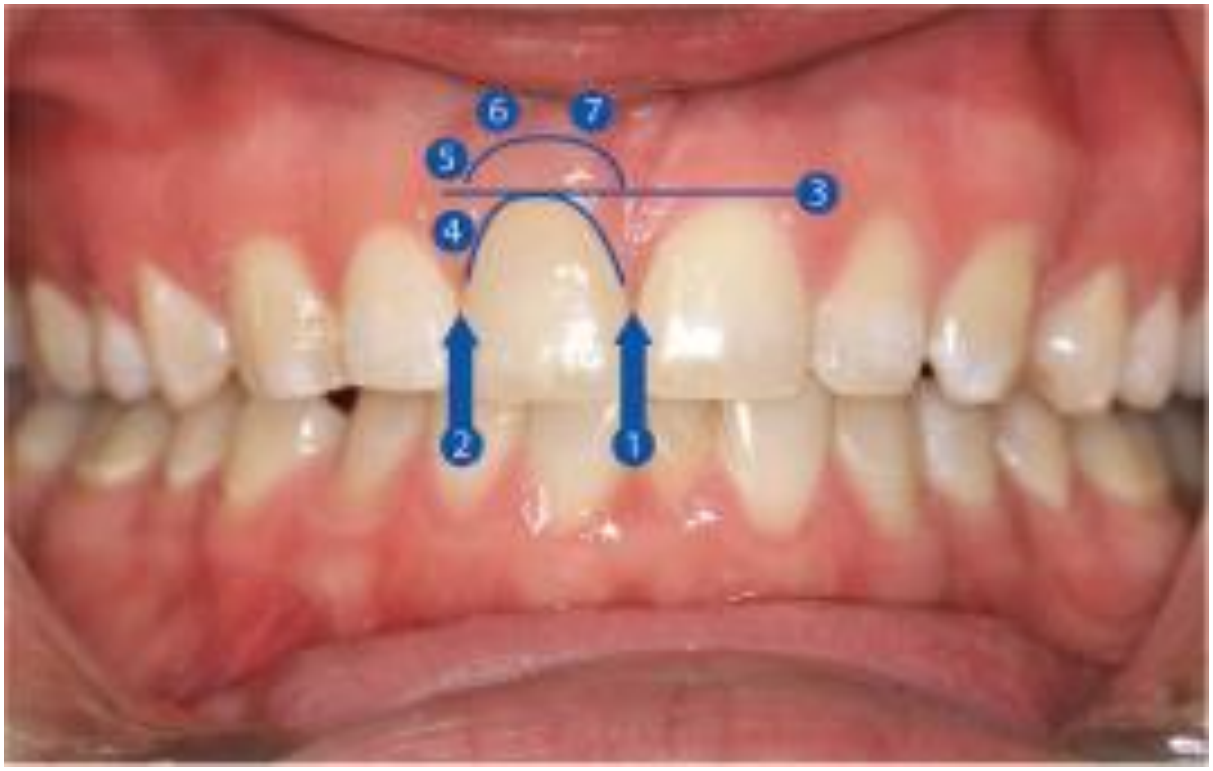
CONSIENTO

En Murcia a ……. de ……. de 2017

Fdo. El Paciente Fdo. Odontólogo

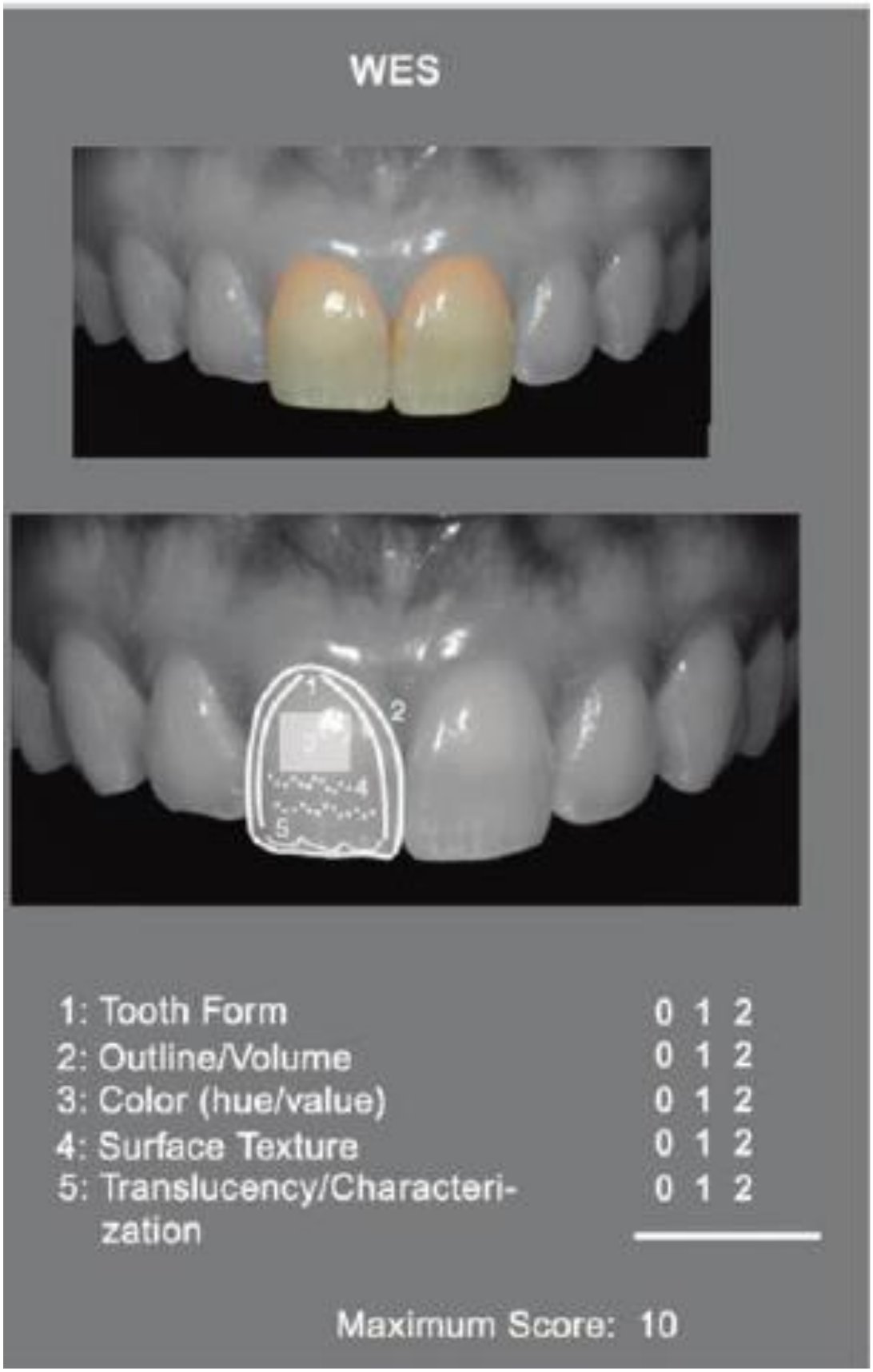
D. …… Dr. ……...

9.4 PES Score variables (Fürhauser et al., 2005).



Variables		0	1	2
Mesial papilla	Shape vs. reference tooth	Absent	Incomplete	Complete
Distal papilla	Shape vs. reference tooth	Absent	Incomplete	Complete
Level of soft-tissue margin	Level vs. reference tooth	Major discrepancy >2 mm	Minor discrepancy 1–2 mm	No discrepancy <1 mm
Soft-tissue contour	Natural, matching reference tooth	Unnatural	Fairly natural	Natural
Alveolar process	Alveolar process deficiency	Obvious	Slight	None
Soft-tissue color	Color vs. reference tooth	Obvious difference	Moderate difference	No difference
Soft-tissue texture	Texture vs. reference tooth	Obvious difference	Moderate difference	No difference

9.5 WES Score variables (Belser et al., 2009).



9.6 Patient's reported outcomes. Survey.

ENCUESTA DE SATISFACCIÓN DEL PACIENTE
(De Bruyn et al., 1997)

Preguntas relacionadas con el implante	**---**	**--**	**-**	**+**	**++**	**+++**
¿Ha tenido dificultades en el habla?						
¿Cuál es su opinión sobre la estética conseguida?						
¿Volvería a someterse a este tipo de cirugía?						
¿Recomendaría este tratamiento?						
¿Considera el implante igual que su propio diente?						
¿Cuál es su opinión sobre las medidas de higiene?						
¿Cómo considera la cooperación cirujano-dentista?						
¿Cuál es su opinión sobre el coste-beneficio?						

(---) Extremadamente negativo
(--) Moderadamente negativo
(-) Ligeramente negativo.
(+) Ligeramente positivo
(++) Moderadamente positivo
(+++) Extremadamente positivo.

9.7 Patient's reported outcomes. Visual Analogue Scale (VAS)

Día de la colocación de la corona definitiva

0	1	2	3	4	5	6	7	8	9	10

A los 12 meses de la colocación de la corona definitiva

0	1	2	3	4	5	6	7	8	9	10

(Valor 0) Estética extremadamente mala
(Valor 10) Estética perfecta