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DOCTORAL DISSERTATION ON SUBCRESTAL IMPLANT PLACEMENT: ANALYSIS OF MARGINAL BONE LEVELS RELATED TO SURGICAL AND PROSTHETIC FACTORS

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LIST OF PAPERS:

This dissertation is based on the following papers which will be classified and referred into the text by their Roman numeral.

I. Lops D, Stocchero M, Motta Jones J, Freni A, Palazzolo A, Romeo E. Five Degree Internal Conical Connection and Marginal Bone Stability around Subcrestal Implants: A Retrospective Analysis. Materials (Basel). 2020 Jul 13;13(14):3123. doi: 10.3390/ma13143123. PMID: 32668745; PMCID: PMC7411692.

II. Lops D, Romeo E, Stocchero M, Palazzolo A, Manfredi B, Sbricoli L. Marginal Bone Maintenance and Different Prosthetic Emergence Angles: A 3-Year Retrospective Study. J Clin Med. 2022 Apr 4;11(7):2014. doi: 10.3390/jcm11072014. PMID: 35407622; PMCID: PMC8999635.

III. Lops D, Romeo E, Calza S, Palazzolo A, Viviani L, Salgarello S, Buffoli B, Mensi M. Association between Peri-Implant Soft Tissue Health and Different Prosthetic Emergence Angles in Esthetic Areas: Digital Evaluation after 3 Years' Function. J Clin Med. 2022 Oct 23;11(21):6243. doi: 10.3390/jcm11216243. PMID: 36362471; PMCID: PMC9654584.

IV. A.Palazzolo, V.De Giovanni, L.Proietto, D.Lops, E.Romeo Implant emergence angle on peri-implantitis: review of the literature and clinical case presentation. Dental Cadmos, 2023 Dec

V. D.Lops, A.Palazzolo, L.Proietto, M.Mensi, S.Calza, E.Romeo Manual and digitally guided surgical technique for replacing single tooth edentulism by means of sub-crestally placed implants. A 3-year parallel randomized clinical study on marginal bone levels stability. Journal of Dentistry,

Submitted

LIST OF ABBREVIATIONS:

MBL	Marginal Bone Level
EMBL	Early marginal bone loss
PPD	Probing pocket depth
mBI	modified Bleeding Index
mPI	modified Plaque Index
GI	Gingival Index
PI	Plaque Index
FMPS	Full mouth plaque score
FMBS	Full mouth bleeding score
PMPR	Professional mechanical plaque removal
IAI	Implant-abutment-interface
ISC	Implant Supracrestal Complex
CM	Cervical Margin
EA	Emergence Angle
EP	Emergence Profile
STH	Soft tissue height
FH	Freehand surgery
GD	Guided surgery
CBCT	Cone beam computed tomography
CAD/CAM	Computer aided design/computer aided manufacturing
DICOM	Digital imaging and communications in medicine
EOS	Extraoral Scanner
mm	millimeter
95% C.I.	95% confidence interval
RCT	Randomized controlled clinical trial

RIASSUNTO

BACKGROUND:

L’inserimento di impianti in posizione subcrestale rispetto alla cresta ossea è sempre più diffuso. Dispositivi biomedici moderni con caratteristiche atte a renderli impiegabili in tale modo sono stati sviluppati per ridurre l’esposizione implantare all’ambiente orale. E’ infatti universalmente riconosciuto che, dopo il posizionamento, gli impianti dentali vadano incontro ad un processo di rimodellamento osseo che ha il massimo impatto clinico a livello della cresta ossea. L’esposizione della superficie implantare nell’ambiente orale è potenzialmente dannosa in quanto l’accumulo di placca batterica su tali superfici può innescare processi infiammatori che nel tempo possono portare alla perdita dell’impianto stesso. Il posizionamento sottocrestale parte dal rationale secondo cui, a patto che una certa quota di rimodellamento osseo crestale non sia evitabile, tale fenomeno rimanga confinato superficialmente in modo tale che l’impianto sia circondato integralmente dall’envelope osseo. Ciononostante, non tutte le sistematiche implantari presenti in commercio possono essere utilizzate in questo modo. Inoltre, in letteratura sono presenti solo pochi studi clinici con follow-up a breve-medio termine. Il primary outcome di questa tesi è indagare i fattori protesici e chirurgici che possono influenzare il MBL a livello di impianti posizionati subcrestalmente.

OBIETTIVI:

Obiettivi generali del presente lavoro sono di presentare la validazione clinica di impianti sottocrestali e di individuare i fattori chirurgici e protesici che possono caratterizzare il MBL. Secondariamente viene valutata la relazione tra il posizionamento sottocrestale e i parametri biometrici peri-implantari. Obiettivi specifici di ciascuno studio: (I.) valutare in modo retrospettivo 410 impianti dentali subcrestali inseriti in 93 pazienti al fine di individuare potenziali fattori associati con la variazione di MBL tramite l'analisi di regressione lineare multipla. (II.) valutare una possibile correlazione tra l'angolo di emergenza protesico (maggiore o minore di 30 gradi) di riabilitazioni fisse avvitate su impianti subcrestali e la profondità di sondaggio. Secondariamente valutare la correlazione tra l'angolo di emergenza e gli indici gengivale e di placca. (III.) valutare retrospettivamente l'angolo di emergenza protesico vestibolare nei settori anteriori rispetto agli indici biometrici peri-implantari di impianti posizionati a livello sottocrestale. (IV.) revisione sistematica della letteratura per indagare il ruolo dell'angolo di emergenza sullo sviluppo di peri-implantite; (V.) studio randomizzato e controllato con follow-up di 3 anni al fine di valutare il MBL di impianti sottocrestali inseriti mediante chirurgia computer guidata statica rispetto a inserimento a mano libera. Secondariamente valutare le complicanze biologiche e protesiche nonché i parametri biometrici peri-implantari.

MATERIALI & METODI, RISULTATI:

Studio IV.: è stata effettuata una revisione narrativa della letteratura per indagare il ruolo dell'angolo di emergenza implantare sullo sviluppo di peri-implantite. La ricerca elettronica è stata eseguita su MEDLINE (PubMed) e Scopus tramite la combinazione di termini MeSH e parole di testo libero combinate tramite operatori booleani (AND o OR). Sono stati selezionati esclusivamente studi in lingua inglese pubblicati fino a Giugno 2022. Sono stati considerati eleggibili studi prospettici, studi retrospettivi e case series con almeno 10 pazienti. Sono stati valutati tutti i modelli di protesi fissa su impianti: corone singole supportate da impianti, protesi parziali fisse e protesi totali fisse. Tramite ricerca elettronica sono stati individuati 264 articoli; sono stati rimossi gli articoli in duplice copia e quelli aventi solamente l'abstract. Dopo screening di titolo/abstract e lettura dei full-texts, sono stati inclusi 5 studi. Gli studi selezionati per la revisione hanno impiegato diversi metodi per la misurazione dell'angolo di emergenza implantare. Katafuchi e Yi hanno misurato l'angolo di emergenza (EA) radiograficamente dall'aspetto mesio-distale. Il risultato è stato una maggiore prevalenza di peri-implantite in caso di EA >30°. Inoue et al. hanno misurato l'EA in direzione mesiale, distale, buccale e linguale su ciascun impianto dentale. Il risultato emerso è stato che la perdita ossea marginale tende a essere minore quando l'EA è compreso tra 20°-40°. Contrariamente, gli studi di Lops ed Hentenaar hanno riportato che EA >30 gradi possano non influenzare la salute dei tessuti peri-implantari nel breve-medio termine (3-5 anni). Studio I.: sono stati valutati retrospettivamente 410 impianti in 93 pazienti con periodo di osservazione da 2 a 9 anni (media 2,72). In totale sono state valutate 164 riabilitazioni protesiche comprendenti corone singole, protesi parziali e/o complete a supporto implantare. E'stato calcolato un MBL medio di −1.09 ± 0.65 mm al baseline (giorno della consegna del manufatto protesico definitivo) e di −1.00 ± 0.37 mm al t1 (ultima visita di follow-up). Il MBL change tra i due timepoints (t0 e t1) è risultato essere di 0.09 ± 0.68 mm. L'analisi di regressione lineare multipla ha evidenziato che la variazione di MBL (MBL change) sia associata a: periodo di osservazione (follow-up cumulativo), posizione subcrestale

dell'impianto al t0 (baseline) e presenza di diabete di tipo 2 (controllato). Studio II.: è stata effettuata una valutazione retrospettiva di 312 impianti in 74 pazienti con follow-up maggiore di 3 anni (media 3.8 ± 1.3 anni). Sono state valutate 34 corone singole, 65 protesi parziali fisse e 12 riabilitazioni fisse di tipo full-arch. E'stata quindi effettuata una valutazione comparativa sulla base dell'angolo di emergenza protesico (EA). Il gruppo 1 comprendente 175 impianti con EA medio di 45 ± 4 gradi versus il gruppo 2 comprendente 137 impianti con EA medio di 22 ± 7 gradi. Il MBL change tra i due gruppi è risultato essere simile (MBL change gruppo 1: 0.06 ± 0.09 mm ; MBL change gruppo 2: 0.06 ± 0.10 mm) e non si sono osservate differenze statisticamente significative. Parallelamente, l'analisi di regressione lineare non ha mostrato associazione tra MBL e variabili quali tipologia di riabilitazione protesica, angolo di emergenza e sito (anteriore versus posteriore). E' stato possibile osservare valori contenuti in termini di modified bleeding index change (0,2 per il gruppo 1 e 0,1 per il gruppo 2) e modified plaque index change (0,2 per il gruppo 1 e 0,2 per il gruppo 2). Non è stata rilevata alcuna differenza statisticamente significativa tra i gruppi. Studio III.: valutazione retrospettiva di 220 impianti dentali inseriti in 57 pazienti con follow-up superiore a 3 anni. E' stato valutato in modo digitale l'angolo di emergenza vestibolare di impianti inseriti in regione incisiva, canina e premolare. Le riabilitazioni protesiche prese in esame consistevano in 34 corone singole e 62 protesi parziali fisse. L'angolo di emergenza vestibolare medio (EA) misurava 46.4 ± 12.2 gradi nel gruppo 1 e 24.5 ± 4.7 gradi nel gruppo 2. E' stata rilevata una differenza in termini di profondità di sondaggio di 0.062 mm maggiore per il gruppo 1 rispetto al gruppo 2. Tuttavia, non si sono osservate differenze statisticamente significative in termini di profondità di sondaggio, indice gengivale e indice di placca tra i due gruppi. Studio V.: è stato condotto uno studio randomizzato e controllato a gruppi paralleli su 60 impianti. Gli impianti inseriti nel gruppo Controllo sono stati posizionati a mano libera mentre gli impianti inseriti nel gruppo Test sono stati posizionati mediante chirurgia computer-guidata statica. L'obiettivo primario è stato di valutare il MBL annualmente a partire dal baseline (T0, giorno della

consegna del manufatto definitivo) fino a 3 anni di osservazione. Non sono state rilevate differenze statisticamente significative tra i gruppi in termini di MBL, PPD, mBI, mPI. Non sono state rilevate complicanze biologiche o protesiche. E' stato valutato il riassorbimento osseo marginale in funzione dello spessore tissutale al momento del posizionamento implantare (STH). Impianti inseriti in siti con tessuti spessi (>3mm) hanno mostrato tra l'inserimento e il carico protesico (T0), una quota di 0,33mm in meno di riassorbimento osseo marginale rispetto ad impianti inseriti in siti con tessuti sottili (<3mm).

CONCLUSIONI:

La presente tesi ha identificato il successo clinico di impianti inseriti a livello subcrestale (1mm) nel breve-medio termine (3 anni di follow-up). Dagli studi osservazionali e di intervento oggetto della presente, sembra che il MBL sia contenuto entro valori più che accettabili se raffrontati ai criteri di successo proposti per le sistematiche implantari moderne. L'angolo di emergenza protesico interprossimale e vestibolare non sembra essere associato in senso peggiorativo al MBL e ai parametri biometrici peri-implantari relativi a placca e sanguinamento. L'inserimento subcrestale in chirurgia computer-guidata statica è comparabile al posizionamento a mano libera per la stessa sistematica implantare.

ABSTRACT

BACKGROUND:

The subcrestal placement of dental implants is becoming increasingly common. Modern biomedical devices with features to make them employable in such a manner have been developed to reduce the implant exposure within the oral environment. Indeed, it is universally recognized that, after placement, dental implants undergo a process of bone remodeling that has the greatest clinical impact at the level of the bony ridge. The exposure of the implant surface into the oral environment is potentially harmful because the accumulation of bacterial plaque on such surfaces can trigger inflammatory processes that, over time, may potentially lead to the loss of the implant itself. Subcrestal placement is based on the rationale that, provided a certain amount of crestal bone resorption cannot be avoided, this phenomenon remains superficially confined. According to this, the implant remains integrally within the bone envelope. Nevertheless, not all commercially available implant systems can be used in such a manner. Moreover, there are only a few clinical studies with short-to-medium-term follow-up in the literature. The primary outcome of this thesis is to investigate the prosthetic and surgical factors that may influence MBL of dental implants designed to be placed subcrestally.

OBJECTIVES:

General objectives of this thesis are: to present the clinical validation of subcrestal implants and to identify surgical and prosthetic factors that may affect MBL. Secondarily, the relationship between subcrestal placement and peri-implant biometric parameters is evaluated. Specific objectives of each study: (I.) To retrospectively evaluate 410 subcrestal dental implants placed in 93 patients in order to identify potential factors associated with MBL variation by multiple linear regression analysis. (II.) To investigate a possible correlation between the prosthetic emergence angle (EA) (greater or less than 30 degrees) of fixed rehabilitations screwed onto subcrestal implants and the peri-implant probing depth. Secondarily, to evaluate the correlation between emergence angle and gingival and plaque indices. (III.) To retrospectively evaluate the impact of vestibular emergence angle (EA) in the anterior zone with respect to peri-implant biometric indices of subcrestally placed implants. (IV.) systematic review of the literature to investigate the role of emergence angle (EA) on the development of peri-implantitis; (V.) A randomized controlled trial (RCT) with 3-year follow-up was conducted in order to evaluate the MBL of subcrestal implants placed by static computer-guided surgery versus freehand placement. Secondarily, to evaluate biological and prosthetic complications as well as peri-implant biometric parameters.

MATERIALS & METHODS, RESULTS:

Study IV.: A narrative review of the literature was performed to investigate the role of implant emergence angle on the development of peri-implantitis. Electronic search was performed on MEDLINE (PubMed) and Scopus by combination of MeSH terms and free text words combined through Boolean operators (AND or OR). Only English-language studies published up to June 2022 were selected. Prospective studies, retrospective studies, and case series with at least 10 patients were considered as eligible. All type of fixed implant-supported rehabilitations were evaluated: implant-supported single crowns, fixed partial restorations, and fixed complete restorations. By electronic search, 264 articles were identified; duplicate articles and those having only the abstract were removed. After title/abstract screening and full-texts reading, 5 studies were included. The studies selected for review employed different methods for measuring implant emergence angle. Katafuchi and Yi measured the angle of emergence (EA) radiographically from the mesio-distal aspect. The result was a higher prevalence of peri-implantitis in cases of EA >30°. Inoue et al. measured EA at the mesial, distal, buccal and lingual directions on each dental implant. The result that emerged was that marginal bone loss tends to be less when EA is between 20°-40°. On the other hand, studies conducted by Lops and Hentenaar reported that EA >30 degrees may not affect peri-implant tissue health in the short to medium term (3-5 years). Study I.: 410 implants were retrospectively evaluated in 93 patients with an observation period ranging from 2 to 9 years (mean 2.72). A total of 164 prosthetic rehabilitations including single crowns, partial and/or complete implant-supported prostheses were evaluated. A mean MBL of -1.09 ± 0.65 mm was calculated at baseline (day of delivery of final prosthetic restoration) and -1.00 ± 0.37 mm at t1 (last follow-up visit). The MBL change between the two timepoints (t0 and t1) was found to be 0.09 ± 0.68 mm. Multiple linear regression analysis showed that MBL change (MBL change) was associated with: observation period (cumulative follow-up), subcrestal implant position at t0 (baseline), and presence of type 2 diabetes (controlled). Study II.: A retrospective evaluation of 312 implants in 74 patients with a follow-up period greater than 3 years

(mean 3.8 ± 1.3 years) was performed). Thirty-four single crowns, 65 fixed partial dentures, and 12 fixed full-arch rehabilitations were evaluated. A comparative evaluation was then performed on the basis of prosthetic emergence angle (EA). Group 1 including 175 implants with mean EA of 45 ± 4 degrees versus group 2 including 137 implants with mean EA of 22 ± 7 degrees. The MBL change between the two groups was found to be similar (MBL change group 1: 0.06 ± 0.09 mm ; MBL change group 2: 0.06 ± 0.10 mm) and no statistically significant differences were observed. In parallel, linear regression analysis showed no association between MBL and variables such as type of prosthetic rehabilitation, emergence angle and site (anterior versus posterior). It was possible to observe small values in terms of modified bleeding index change (0.2 for group 1 and 0.1 for group 2) and modified plaque index change (0.2 for group 1 and 0.2 for group 2). No statistically significant difference was found between the groups. Study III.: Retrospective evaluation of 220 dental implants placed in 57 patients with follow-up of more than 3 years. The vestibular emergence angle of implants placed in the incisor, canine and premolar regions was evaluated digitally. The prosthetic rehabilitations consisted of 34 single crowns and 62 fixed partial dentures. The mean vestibular emergence angle (EA) measured 46.4 ± 12.2 degrees in group 1 and 24.5 ± 4.7 degrees in group 2. A difference in probing depth of 0.062 mm was found to be greater for group 1 than for group 2. However, no statistically significant differences in probing depth, gingival index and plaque index were observed between the two groups. Study V.: A randomized, controlled parallel-group study on 60 implants was conducted. Implants placed in the Control group were positioned freehand while implants placed in the Test group were inserted by static computer-guided surgery. The primary objective was to evaluate the MBL annually from baseline (T0, day of delivery of the final prosthesis) to 3 years of observation. No statistically significant differences were found between the groups in terms of MBL, PPD, mBI and mPI. No biological or prosthetic complications were detected. Marginal bone resorption was evaluated as a function of tissue thickness at the time of implant placement (STH). Implants placed in sites characterized by thick tissues (>3mm)

showed, on average, 0.33mm less marginal bone resorption than implants placed in sites with thin tissues (<3mm) between the day of implant placement and the prosthetic loading (T0).

CONCLUSIONS:

The present thesis supports the clinical success of subcrestally placed implants (1mm) in the short to medium term (3-year follow-up). From the observational and interventional studies which were mentioned above, it seems that the MBL is contained within more than acceptable values when compared to the proposed success criteria for modern implant systems. Interproximal and vestibular prosthetic emergence angle seems not to be associated with MBL and peri-implant biometric parameters related to plaque and bleeding. Subcrestal placement by static computer-guided surgery is comparable to freehand placement for the same implant system investigated in this set of studies.

INTRODUCTION

MARGINAL BONE LEVELS:

The stability of marginal bone levels around dental implants has always been considered as pivotal to define long-term efficacy of the restorative treatment. After prosthetic loading, peri-implant crestal bone undergoes a remodeling process characterized by multifactorial etiology and variable entity (Stacchi et al. 2023). At the time of writing, this noninfective process is called early marginal bone loss (EMBL). Several surgical and prosthetic variables have been proposed in the literature to explain this phenomenon, such as: insufficient width of the bone ridge and/or implant malpositioning (Spray et al. 2000; Grunder et al. 2005; Chen et al. 2007), surgical trauma (Albrektsson et al. 2017; Coyac et al. 2019), supracrestal tissue height adhesion (Hermann et al. 2000; Spinato et al. 2022), overload (Misch et al. 1999), polished implant neck (Wiskott et al. 1999), microleakage and bacterial accumulation at the implant-abutment microgap (Ericsson et al. 1992; Jansen et al. 1997; Piattelli et al. 2003), presence of platform-switching (Baffone et al. 2012; Atieh et al. 2010), repeated abutment disconnection/reconnections (Tallarico et al. 2018; Vatenas et al. 2021), prosthetic abutment material (Abrahamsson et al. 1998), prosthetic abutment height (Galindo-Moreno et al. 2014; Blanco et al. 2018), implant-abutment connection mechanical stability (Liu et al. 2017) and structural bone adaptation to functional loading (Oh et al. 2002). Throughout the years, an early marginal bone loss up to 1.5–2 mm followed by a maximum of 0.2 mm annually thereafter, was commonly considered a defining criterion of implant success (Papaspyridakos et al. 2012). Nevertheless, the notion of clinical success in dental implantology has changed in recent years and an early marginal bone loss <0.5 mm is nowadays accepted as a threshold between peri-implant bone physiological remodeling and a borderline condition potentially leading to subsequent peri-implant pathology (Windael et al. 2018). In this regard, a recent prospective study at 10 years conducted by Windael et al. in 2021 showed that implants with EMBL ≥0.5 mm had 5.43 times higher odds of future peri-implantitis development than implants with EMBL <0.5 mm during the first year of function (Windael et al. 2021). Recent literature suggests that limiting EMBL may improve long-term efficacy of implant treatments. Accordingly, Galindo-Moreno et al. reported that EMBL >0.44 mm after 6 months of prosthetic loading was an important predictor of marginal bone loss >2mm after 18 months of observation (Galindo-

Moreno et al. 2016). Furthermore, it has to be highlighted that the stability of peri-implant mucosa surrounding implants is strongly dependent on the level of the underlying bone. As a consequence, the apical migration of the marginal peri-implant mucosa may have several implications in the aesthetics of the rehabilitation, especially in the anterior zone. Hence, the identification of the causes leading to early marginal bone loss seems to be of uttermost importance in modern dental implantology.

DETERMINANTS OF CRESTAL BONE STABILITY:

As previously stated, in modern implantology, the importance of crestal bone stability around osseointegrated implants is a crucial aspect regarding the success and longevity of the entire treatment plan. In this context, radiography performed using the parallel beam technique is the tool of choice for measuring the quality of the treatments. It is widely accepted among clinicians that stable bone level around implants is a measure of long-term treatment success along with the absence of bleeding/suppuration and probing depths exceeding 5-7 mm. On the other hand, peri-implant marginal tissue instability can generate problems and leave clinicians in uncertainty about the prognostic expectation of each implant affected by this condition. The concept of "crestal bone level" has accompanied implant treatment since its earliest days to the extent that it has been considered the norm and has been classified in various ways. For example, the so-called "early crestal bone loss" is defined as the bone resorption that occurs around the implant neck in the period between placement and 1 year after prosthetic loading. This concept was developed from the observation of dental implants of the original "Branemark type". In this regard, it should be considered that the implant systematics used in contemporary implantology have design and surface characteristics that lead to greater success and bone stability. For this reason, some recent studies have challenged the "classical" success criteria since it is possible for many modern implant systems to exhibit less resorption one year after prosthetic loading (Papaspyridakos et al. 2012). In the literature, early crestal bone loss is sometimes described as " bowl-like," "crater-like," or "ditch-like" based on the pattern of bone resorption seen on x-rays. This pattern of resorption has historically been considered a natural and inevitable biological process as well as probably related to bone density. Over the years, occlusal trauma has also been suggested as a possible cause. Nevertheless, several authors have criticized this hypothesis since it does not explain why overloading at the implant collar can cause bone resorption that tends to self-limiting over time and not progressing to complete failure of the fixture. Other authors, to explain this phenomenon, have suggested that in the early stages of prosthetic loading the bone is less dense and more susceptible to stresses. This condition would change within the first year of loading since bone maturation would lead to an increase in density such that the loading forces responsible for the initial bone resorption would no longer be able to cause further resorption.

Despite the proposed theories and constant innovation in terms of techniques and materials, the problem of peri-implant bone resorption is still encountered in everyday clinical practice. In fact, several authors have proposed that the idea of considering 1/1.5 mm bone loss as normal should not be considered valid in the future. In fact, it has been noted that in the presence of implant fixtures, bone tissue may show different reactions including:

- Absence of bone resorption ("no bone loss"): represents "crestal bone stability" or the lack of momentary or permanent bone loss after implant placement. For implant rehabilitation it is the gold standard namely the aim of every clinician.
- Stable remodeling ("stable remodeling"): refers to an initial bone loss that tends to stop without further progression over time. It can be determined by biological or mechanical factors. In any case, self-limiting bone loss is not in itself a risk factor for implant survival. Nevertheless, it would be best to avoid this condition because apical migration of the attachment apparatus can easily promote the emergence of an anaerobic environment that is difficult to manage. This is pivotal because of the patient's possible predisposition to periodontal disease or possible reduced performance in terms of home hygiene or reduced "adherence" to the individualized maintenance and support protocol.
- Progressive bone resorption ("progressive bone loss"): is a critical condition characterized by the triggering of bone resorption that does not tend to self-limit and can lead to major aesthetic and functional complications. It is not possible to predict the evolution of this scenario, which can lead to implant loss.
- Demineralization and Remineralization: bone tissue may behave variably according to different stages of healing and tissue remodeling. In this context, demineralization and remineralization phenomena may be observed. In fact, radiographic crestal bone resorption may not be "true" bone resorption but demineralized organic matrix. The tool for assessing marginal bone levels is in fact

two-dimensional radiography in which demineralization and bone loss can be confounded. This phenomenon has also been described in classical periodontology studies concerning occlusal trauma. Indeed, Rosling and coworkers in 1976 observed regeneration of intrabony defects in patients capable of maintaining optimal plaque control. The removal of bacteria and irritants would thus promote remineralization of the bone matrix. This phenomenon can also be observed at the level of implants of previous generations characterized by the lack of platform-switching. Indeed, several clinical observations have shown that once the prosthetic finalization phase is completed, an "undisturbed" environment can promote the conditions for remineralization (Qian et al. 2012).

- Corticalization: occurs when the peri-implant cortical tissue appears denser or mineralized. The radiographic appearance shows an increase in white levels as well as bone height after prosthetic loading. The reason for this phenomenon is not fully understood although it can be explained by Frost's mechanostatic theory that states the possibility of increased mass in the presence of moderate and constant overload. This phenomenon also occurs when crestal interference to implant placement is surgically reduced. In fact, several authors assert that healing in medullary bone would be preferred because there is a greater capacity for revascularization and would also allow for a reduction in crestal necrosis.
- Bone growth: to date, there are no studies that have demonstrated a predictable process for achieving bone growth over the implant shoulder after the surgical and prosthetic phases. Nevertheless, it has been reported that constant loading in the absence of inflammation can lead to progressive induced bone growth. These data offer a different and encouraging view by suggesting that improvement over time is possible, even with initial bone loss.

Although stability of crestal bone tissue should be achieved in every implant rehabilitation, there are two clinical situations that require "as coronal as possible" bone maintenance as an absolute prerogative, namely implant placement in the esthetic area and the need to use implants of short length (<8 mm). From a purely scientific point of view, it is important to understand the etiopathogenetic mechanism of crestal bone resorption. Although many factors have been proposed and analyzed in the literature, to date the issue remains controversial. Indeed, some of these factors are strictly operator-dependent such as: incorrect three-dimensional placement, surgical trauma, reduced inter-implant distance, not due supracrestal placement or excessive insertion torque. Another important factor to consider is bacterial control of the oral cavity as both appropriate periodontal disease therapy and plaque control should be achieved before implant placement. Another crucial aspect is related to the implant design and the presence of a microgap at the fixture-abutment level.

MICROGAP:

It seems logical that every "two-piece" implant has a microgap, namely an interface zone between fixture and abutment. This interface is of paramount importance and plays a crucial role in terms of implant stability. Some clinicians prefer the usage of "one-piece" implants, which in fact bypass the microgap concept. In theory, such implants should not show crestal bone loss associated with the effects of fixture-abutment junction localization. Nonetheless, from the studies available to date, it cannot be stated that "one-piece" implants have lower levels of crestal bone loss. Microgap has been associated with crestal bone loss, and all modern implant systems have this feature due to the fact that the 2-component design provides flexibility in prosthetic-restorative treatment and ample prosthetic freedom to the clinician, who thus has the option to choose based on the clinical conditions. In parallel, the presence of microgap is closely related to the use of "two-piece" implants and that the latter are the most widely used system to meet everyday clinical needs. The influences of this factor on crestal bone maintenance have probably been among the most discussed in the implant literature. Numerous studies have been conducted with pre-clinical and clinical experimental models that have fueled a great deal of scientific and clinical interest regarding this topic. To fully understand what is the relationship between implant-abutment connection and crestal bone stability, the microgap needs to be analyzed from two different perspectives namely, 1) as a source of bacterial contamination/percolation, 2) as a source of micromovement.

MICROBIAL PERCOLATION:

"Two-piece" implants inevitably encounter internal bacterial colonization, and such an occurrence can occur 1) at the time of implant placement, 2) during prosthetic phases, and 3) due to unscrewing after a period of functional loading. An important factor is definitely the size of the microgap. Several laboratory studies have shown that there is great variability in microgap depending on different implant systematics and abutments. Kano and coworkers in 2007 reported a horizontal misfit of IAI between 75 and 103 microns depending on the type of abutment while the vertical gap was found to be smaller varying between 0 and 11 microns (Kano et al. 2007). Other studies have shown that the IAI represents a "gateway" for bacterial contamination, which in the case of extensive fissuring can lead to contamination of the entire implant. Stability: stability of IAI is another key factor since micromovement can generate fluid flows associated with bacterial biofilm that can trigger an inflammatory process. It should be noted, however, that micromovement, per se, could be deleterious at the bone level. Among the different types of connections (external, internal, flat, geometric, etc...) the tapered type showed less micromovements under load simulation (Figure 1). Such stability would be sought in every rehabilitation, especially in case of subcrestal placement of the fixtures. Hermann and coworkers conducted a study to investigate the etiology of early marginal bone loss. This trial involved the placement of 60 implants in 5 dogs (hound breed). The first two groups of implants had a microgap of 50 and 100 microns, respectively, while the third group consisted of implants whose abutment was joined to the respective fixture by "laser-welding" and thus preventing any movement between the components. Thus it was possible to observe that the first two groups had statistically significant levels of crestal bone loss compared with the laser welded group. Based on this, the authors concluded that the micromovement probably has a greater relative importance than the magnitude of the microgap itself. IAI instability is believed to have a twofold effect on crestal bone level. First, the micromovement generated under functional (especially nonaxial) loading produces a kind of "pumping effect" in which microorganisms continuously pass from the oral environment to the inner portion of the implant system. This action contributes to the formation of the inflammatory infiltrate that forms the rational basis for explaining the bone resorption associated with microgap (Hermann et al. 2000). Another theory states instead that micromovement per se can induce direct

osteoclastic activation and resorption of bone located in close proximity. Ericsson and coworkers called such a histologic picture "abutment-infiltrated connective tissue" and suggested that this situation represents an adaptive host response to infection. Such infiltrate would therefore be a protective mechanism for peri-implant tissue (Ericsson et al. 1996). The pathogenesis of microgap-related bone loss has been described by Broggini et al. (Broggini et al. 2006). The pattern of neutrophil accumulation suggests a chemotactic stimulus that originates near the IAI and triggers the recruitment of other inflammatory cells. Such cells would then promote the formation of osteoclasts, which in turn would cause alveolar bone loss.



Figure 1: Implant section showing features of the internal connection, Koutouzis et al. 2019)

PLATFORM SWITCHING & MICROMOVEMENT:

Osseointegration, in its establishment and maintenance phases, is a dynamic process. The establishment phase is characterized by simultaneous processes of bone resorption in the regions of contact between the implant surface and bone gaps, and neo-formation of bone matrix in the areas without contact. In the maintenance phase, however, osseointegration is ensured by continuous adaptation and remodeling. Many factors influence the osseointegration process. Among them, microstructural and implant design characteristics (macrostructure) can be distinguished. The term microstructure refers to the treatment of the implant surface, while macrostructure refers to characteristics such as shape, length and diameter. Most crestal bone loss occurs during the first year of functional loading. This resorption begins at the time of implant placement and is attributable to surgical trauma, prosthetic overloads, peri-implantitis, biological width formation, macroscopic and microscopic features of the implant neck, the structure of the abutment-implant connection, and the location of the microgap. Generally, peri-implant bone remodeling has been termed "at the first thread," positioning itself approximately 2 mm apically from the implant-abutment interface (IAI), while soft tissue interfaces with the implant margin. Excessive loss of marginal bone tissue results in loss of the interdental papilla with negative sequelae on the aesthetics of the entire treatment. To reduce peri-implant bone loss, the concept of platform switching was developed. Platform switching has been reputed as one of the main innovations concerning the design of implant systematics introduced on the market. The logical rationale lies on the possibility of moving the bacterial "leakage" interface horizontally away from the area of the first vertical "bone-to-implant contact." This situation is made possible when an implant abutment of reduced size relative to the implant head is employed (Figure 2 and 3). This configuration allows extension of the biological width horizontally. Lazzara and Porter in a study conducted in 2006 (Lazzara RJ, Porter SS 2006) hypothesized that moving the implant-abutment junction inward may move the inflammatory infiltrate away from the bone crest thus limiting resorption. The achieved reduction in bone loss appears to be related to the extent of fixture-abutment size mismatching. Canullo and coworkers in a prospective study of 69 implants in 31 patients observed bone resorption of 1.49 mm in implants without platform-switching, 0.99 mm in the presence of 0.2 mm distance from IAI, 0.82 mm at 0.5 mm from

IAI, and 0.56 in the case of 0.85 mm from IAI. Thirty-three months after the surgery, it was observed that the effect of platform switching on crestal bone preservation was greater as the abutment-shoulder distance of the fixture increased. Similarly, Vela-Nebot and coworkers studied the crestal bone stability of implants with platform-switching of 0.45/0.5 mm (test group) versus implants without platform-switching (control group) (Vela-Nebot et al. 2006). Follow-up radiographic examination at 1 year showed the following values: mesial aspect mean MBL 2.53mm control group versus 0.76mm test group: distal aspect mean MBL 2.56mm control group versus 0.77mm test group. The authors concluded that implants with platform switching exhibit a significant reduction in bone loss compared with the control group. In 1991, implants with larger diameters than the conventional ones (5 and 6mm) were introduced on the market, but without adjusting the diameter of the abutments. Subsequently, it was randomly observed that the use of this method reduced bone ridge resorption. The image shows the difference between standard (matching-connection) and platform-switching fixture-abutment coupling and the related benefits to the bone ridge. Vigolo and Givani in 2009 compared the bone resorption at the load of implants with reduced abutment size and implants with standard abutment-implant interface; 182 implants (85 standard and 97 platform-switched) were placed in 144 patients at the posterior sectors of both arches (Vigolo et al. 2009). At one year after loading, peri-implant bone resorption was 0.9±0.3 mm for the standard group and 0.6±0.2 mm for the platform-switched group; five years after loading, peri-implant bone loss was 1.1±0.3 mm and 0.6±0.2 mm, respectively. The authors concluded that the platform-switching system leads to less marginal bone loss and that the difference was statistically significant at one year after prosthetic loading.

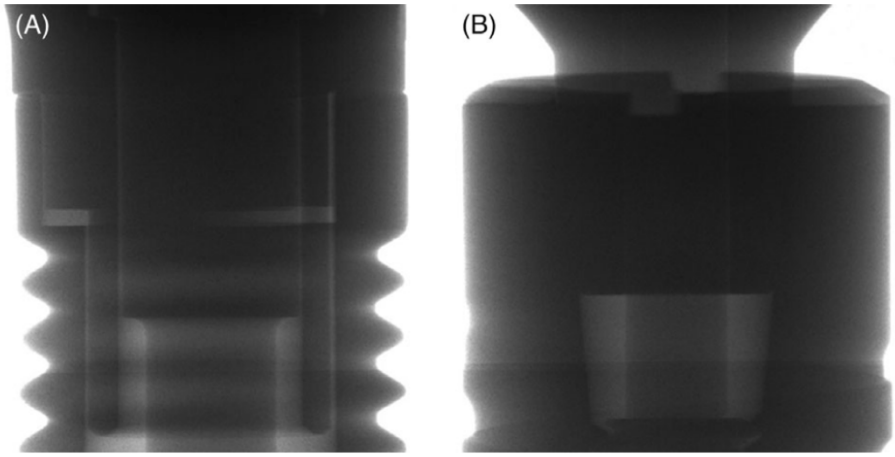


Figure 2:

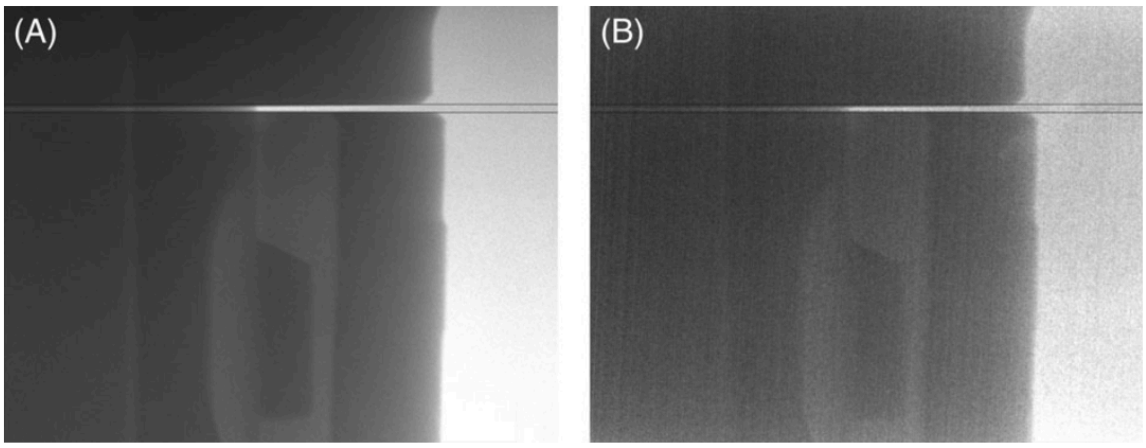


Figure 2 and 3: Platform-switching and micromovenet at flat-to-flat connections, from Zipprich et al. 2018).

SUBCRESTAL IMPLANT PLACEMENT:

According to the dental literature, dental implants can be placed in different position in relation to the bone crest, namely: at the crestal level (crestally), above the bone ridge (supra-crestally) or apical to the surrounding bone levels (sub-crestally) (Esposito et al., 2014). Subcrestal implant placement is a clinical strategy aimed at reducing the risk of implant surface exposure as a consequence of MBL. In this regard, Linkevicius et al. claimed that, when the platform of the implant is placed in subcrestal position, MBL might occur either only above the implant shoulder (this process is called bone remodeling) or may extend beyond the bone surrounding the implant neck and underlying implant surface (bone loss) (Linkevicius et al. 2020). It seems logical that anticipating crestal bone remodeling by modulating the vertical position of the implant head in relation to the bone crest may confine bone remodeling above the fixture, thus avoiding direct exposure of the implant surface in the oral environment (Vervaeke et al. 2018; Doornewaard et al. 2020). Nonetheless, currently, the relationship between marginal bone stability and subcrestal implant placement is still a matter of debate among clinicians and researchers. In this regard, whether several authors reported that subcrestal implant positioning up to 2 mm might exhibit reduced crestal bone remodeling (Aimetti et al. 2015), others observed that early marginal bone loss may be aggravated by implant deepening (Koutouzis et al. 2013; Lombardi et al. 2019). Infact, studies aimed at comparing subcrestal versus equicrestal implant positioning reported higher MBL in case of subcrestal implant placement (Al-Amri et al. 2016; Gatti et al. 2018). In a meta-analysis published by Silva Cruz et al. in 2022, the authors concluded that subcrestal implants showed comparable results (no significant differences) to implants placed crestally in terms of MBL and survival. The authors attributed this result, differently from previous systematic reviews and meta-analyses, to the presence of platform-switching and rough surface in all the included studies. Moreover, even if some studies observed that subcrestal implant placement should be preferred to favor soft tissue parameters, this study reported no relationship between the soft-tissue parameters and the placement depth. Among other limitations, the authors reported an unclear or high risk of bias in the blinding of participants and outcome assessment when evaluating the quality of the included RCTs. In addition, no sub-analysis was performed on other important aspects such as: surgical technique,

bone quality, insertion torque. All included studies were characterized by a short follow-up (mainly 1 to 3 years, only 1 study presented 5-year follow-up data). Then, the authors raised the problem related to the clinical limitation regarding the position of the implant because the reference used during placement at the buccal, lingual, mesial, or distal levels could be subcrestal in a specific area (such as buccal), but at crest level in another area (Silva Cruz et al. 2022). This shortcoming is strictly related to the fact that the bone anatomy is not planar. In this regard, it should be highlighted that determining the precise location of the implant in advance by digital planning and guided surgery may simplify the investigation of such events. These authors encouraged further studies featured by adequate sample size, methodology (RCT) and follow-up to reassess and compare the results obtained in their meta-analysis.

COMPUTER GUIDED SURGERY:

Nowadays, two typologies of guided implant placement protocols, namely static and dynamic, are available on the market. The static guided surgery consists of using a static surgical guide. It is possible to transfer the digital implant location directly from computerized tomographic data to a surgical template (Boldt et al., 2009). The surgical jig may be produced through cad/cam technology by a specially designed drilling machine (Sailer et al., 2012) or by the stereolithographic method (using polymerization of an ultraviolet sensitive liquid resin) (Cooper et al., 2019). The dynamic methodology is also called navigation implant surgery. This system is based on the motion tracking technology that provide real-time tracking of the dental drill and the patient throughout the surgical intervention. The main difference from static systematics is the possibility to make positioning changes according to surgical needs.

Static computer-guided surgery represents an alternative implant placement procedure that has seen rapid development in recent years both in terms of operative technique and predictability of results. Through this computerized implant placement planning procedure, and to the transfer of digital information for the execution of clinical guides for implant surgery, pre-surgical implant planning is possible (Vercruyssen et al., 2014). This operative approach can represent an improvement in many aspects regarding implant placement: morbidity for the patient (as flap-less surgery can be performed or, alternatively, minimizing the 'extension of surgical flaps), execution time (planning allows implant placement exactly where planned), and reduction of surgical error related to subjective operator activity (Schneider et al., 2009). Guided surgery may also be particularly useful in cases of reduced tissue volumes and/or where there is a need for implant placement that is to be considered ideal from both an esthetic and functional (prosthetically guided) viewpoint. Such technology can also avoid or limit extensive bone regeneration procedures, reduce bacteremia, facilitate immediate loading procedures, and make the therapeutic design clearer to patients' perspective (D'haese et al. 2012; Arisan et al. 2013). Nevertheless, the introduction of new technologies raises important questions about their impact on survival and long-term success in implantology as well as their impact on peri-implant biometric parameters and their maintainability over time. In parallel, given that the

peri-implant mucosa and its circumferential adhesion (the so-called "peri-implant seal") is constantly challenged by the oral environment (Tomasi et al., 2016), the role of bone remodeling from implant head exposure and its influence on tissue stability over time need to be better clarified. In this regard, some procedural aspects such as the risk of less irrigation of the operative site may produce damage to the recipient bone during guided surgery procedures due to the encumbrance of surgical templates (Dos Santos et al., 2013). Unfortunately, in the current state of affairs, there is no unanimous consensus regarding crestal bone changes following implant placement by guided surgery. What is certain is that bone necrosis due to overheating of the implant site is a clinical situation that should be given adequate attention. In this regard, a study conducted by Misir et al. showed that the use of surgical guides for implant site preparation produces significantly more heat than freehand placement regardless of the irrigation system examined. Moreover, this finding was statistically significant for each preparation depth evaluated in the statistical analysis i.e., 3, 6 and 9 mm, respectively (Misir et al., 2009). Similarly, Dos Santos and coworkers, using an experimental animal model, concluded that the "classical" procedure of implant site preparation is more respectful in terms of cell viability when compared to guided surgery (Dos Santos et al., 2013). The consequence of overheating may be more peri-implant bone remodeling related to this procedure when compared with conventional freehand implant placement. In a recent systematic review of the literature, it was concluded that the certainty of this risk in guided surgery is not demonstrable due to the lack of mid- to long-term clinical data (Carbajal Mejia et al., 2016).

R2GATE SYSTEM:

R2Gate® (Megagen implants, Daegu, South Korea) is the guided surgery system used in Study V. (Figures 4 & 5). The peculiarity of this system is that surgical guides are sleeveless, printed entirely in resin, namely without the presence of metal sleeves. This is the main difference when compared to other systems. Furthermore, R2Gate® guides are keyless, namely without any stop or reducer. The rationale behind such sleeveless and keyless methodology is to simplify the surgical procedures. Indeed, all the information relating to the sleeve, the stops for implant bed preparation and the reducers are included within the sequence of surgical burs. In addition, the digital planning software is featured by a tool called "Digital Eye" which allow to evaluate, in advance, the bone density at each implant site. On this basis, the surgeon could modulate the drilling sequence in order to reach primary stability according to implant location and available tissue volumes. (Cristache & Gurbanescu, 2017; Cristache et al., 2021)

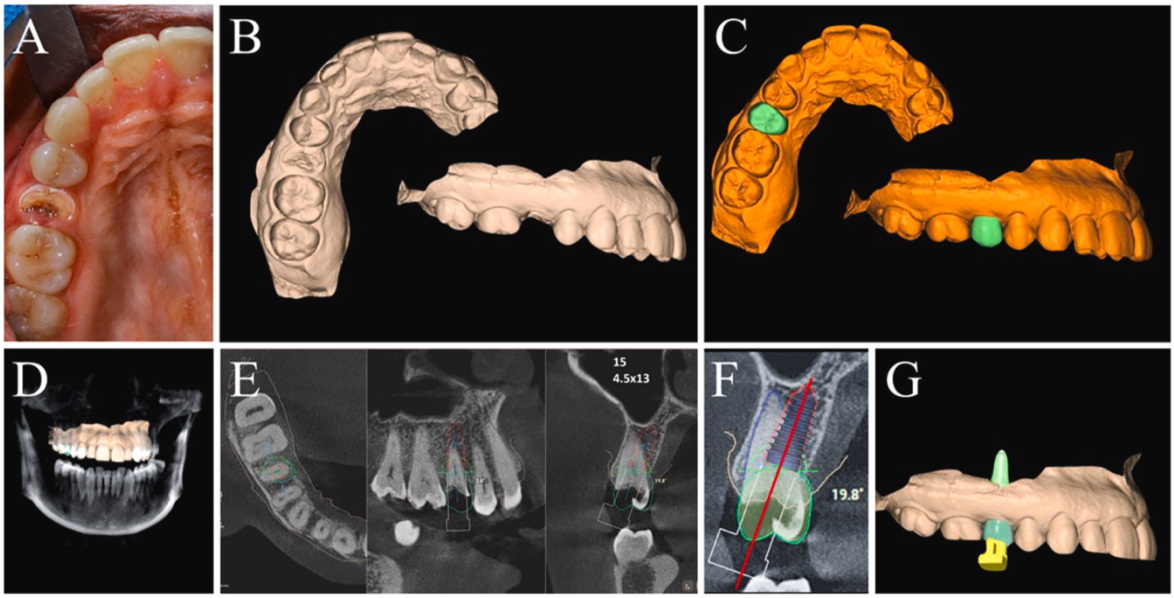


Figure 4: Immediate restoration in the posterior maxilla with R2Gate®. (A) Pre-operative occlusal view of the patient. A single broken tooth (right second premolar, #15) must be replaced with an immediate dental implant. (B) Intraoral scan. (C) Digital waxing. (D) CBCT and intraoral scan merging with the waxing in evidence. (E) Implant planning with R2Gate®: the implant position, depth and inclination is carefully studied and it represents the best possible compromise between the ideal emergence profile given by the prosthetic virtual waxing and the available bone volume in the post-extraction case. (F) The position of the implant is extracted virtually for the immediate temporization. From Chandran et al. 2022



Figure 5: Details of the surgical planning through R2Gate system. From Chandran et al. 2022

IMPLANT SUPRACRESTAL COMPLEX, EMERGENCE PROFILE AND ANGLE:

Recently Mattheos et al. introduced the concept of the Implant Supracrestal Complex (ISC). The authors described the critical elements that define it as a unique anatomic, and functional system of human tissues, mechanical components and oral bacteria / biofilm (Mattheos et al., 2021). This article shed light on the fact that the dimensions of the peri-implant mucosa is strictly associated with the features and peculiarities of the prosthetic shape. According to this statement, the authors support the concept that these factors cannot be studied as isolated variables. Three critical design features characterizing ISC were identified, namely: the emergence profile (EP), emergence angle (EA) and the cervical margin (CM). The cervical margin of the restoration (CM) is referred to as the circumferential boundary line between the most coronal border of the peri-implant mucosa and the most apical visible portion of the prosthesis (Figure 6). As far as natural teeth are concerned, the Cervical Margin basically coincide with the most coronal part of the periodontal sulcus. Conversely, in implant supported rehabilitations, the CM is mainly related to a prosthetic notion. Indeed, it can be defined as the visible portion of the implant restoration at the interface with the peri-implant soft tissue.

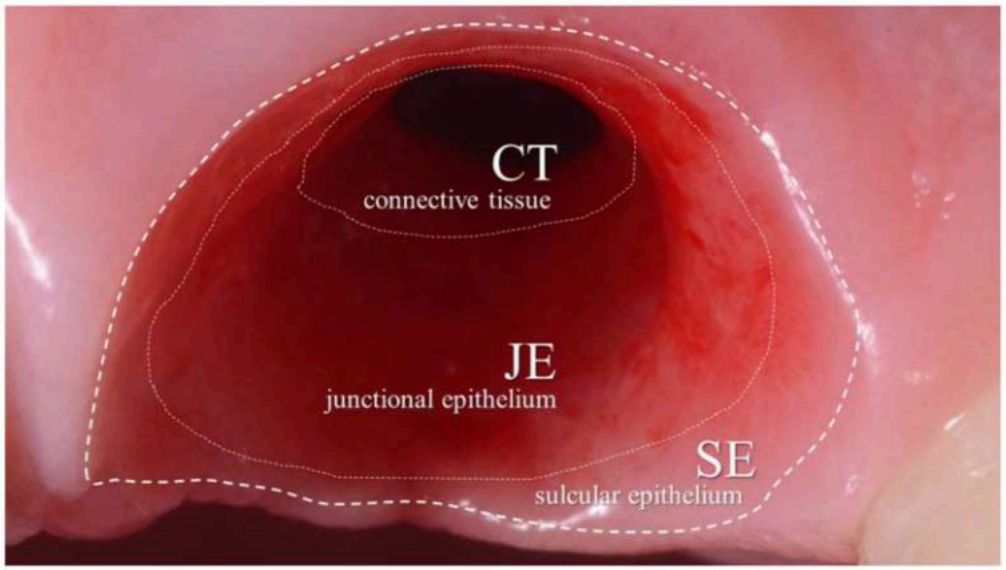


Figure 6: This figure illustrates the peri-implant transition zone which includes: the connective tissue zone, the junctional epithelium zone and the sulcular epithelium. The outermost portion of the dotted line delimiting the sulcular epithelium is referred to as the “cervical margin”.

In the last version of The Glossary of the Prosthodontic Terms , the emergence angle (EA) was defined as the angle between the average tangent of the transitional contour relative to the long axis of a tooth, dental implant or dental implant abutment (Driscoll et al. 2017). This technical notion is of utmost importance due to the fact that when restoring dental implants, a horizontal discrepancy between the implant diameter and the final prosthetic restoration needs to be compensated (Testori et al. 2018). At the same time, several studies have investigated the role of overcontouring on plaque accumulation that, consequently, could lead to gingival inflammation (Jeffcoat et al. 1980; Pack et al. 1990). Indeed, especially in the gingival third, a proper oral hygiene could be hindered. From historical perspective, regarding tooth-borne protheses, already in 1973 Yuodelis et al. pointed out that “overcontouring […], encourages the accumulation of particulate and microbial matter in an area inaccesible for cleaning by the patient” (Yuodelis et al. 1973). In parallel, Becker and Kaldahl stated that “overcontouring is a greater periodontal hazard than undercontouring” (Becker & Kaldhal 1981). Moreover, greater marginal bone loss and change in subgingival microflora have been related to bulky restorations (Lang et al. 1983). Suboptimal oral hygiene aroud dental implant has also been associated with peri-implantitis (Ferreira et al. 2006). Indeed, peri-implantitis is defined as an infectious disease triggered by bacteria from the dental biofilms and followed by a local host response that is characterized by inflammation in the peri-implant mucosa and subsequent progressive loss of supporting bone (Berglundh et al. 2018; Lang et al. 2011). It has been recommended that the implant–abutment–prosthesis complex should be shaped in order to guarantee adequate access both for continuous monitoring (probing) and plaque removal (Mattheos et al. 2021). To this purpose, Monje et al. reported that 77.2% of the peri-implantitis cases showed inadequate access for cleanability (Monje et al.

2019). As a matter of fact, it has been highlighted that the current prevalence of peri-implantitis after 5 years is 18.8% at patient level (Atieh et al. 2013). In recent years, as far as dental implants are concerned, Katafuchi et al. suggested that over-contoured restorations characterized by wide emergence angle (>30°) are more prone to undergo peri-implantitis. Owing to a mismatch between the implant head and abutment, the authors speculated that platform-switching implants might necessitate wider emergence angle that, in turn, could increase the risk of peri-implantitis. On the contrary Hentenaar et al. recently observed no peri-implantitis when investigating posteriorly placed platform-switching implants characterized by small emergence angles (<20°). In this scenario, a recent systematic review and meta-analysis was published by Atieh et al. The main goal of this study was to compare implant restorations with emergence angle of >30° to those with emergence angle of ≤30° in terms of changes in peri-implant marginal bone level, modified bleeding, and plaque indices and prevalence rate of peri-implantitis after at least 3 years of functional loading. (Atieh et al. 2023). The authors concluded that radiographic changes in marginal bone levels were not influenced by the restorative emergence angle. Nevertheless when the analysis excluded the study conducted by our group (Lops et al. 2022) the difference was statistically significant in favor of the restorative emergence angle of ≤30. In this regard, it is crucial to highlight that previous studies have reported data on old-fashioned implant systems. In some cases (as in the study conducted by Katafuchi), reported data included cemented prostheses, implants with external platform-matched connections, smokers and patients with a history of periodontitis. The usage of systematics characterized by precise connection, the strict inclusion and exclusion criteria and the use of screw-retained prostheses could, at least in part, explain this difference. Indeed, the authors reported that the difference in prevalence rates of peri-implantitis among implant restorations with emergence angle of >30° and ≤30° was barely significant ($p = 0.05$). On the contrary, it seemed that implant restorations with convex emergence profile (frequently associated with mechanical hindrance towards daily oral hygiene maneuvers) had significantly higher prevalence rate of peri-implantitis compared to those with concave or straight emergence profile ($p = 0.02$). In this scenario, the authors raised the hypothesis that the presence of platform-switching might be, per se, a key factor determining bone stability irrespective of the emergence profile or angle that had been

employed. Nevertheless, at the current state of affairs, the scientific evidence behind the role of EA on plaque accumulation, mucosal inflammation, peri-implantitis and marginal bone loss is low. Future studies with careful control of confounding variables and with adequate methodology, sample size and follow-up are warranted.

SOFT TISSUE HEIGHT (STH):

Over the years, soft tissue thickness has been mainly investigated from the perspective of the horizontal aspect. Lot of studies and treatment techniques have been proposed to improve the facial contour around implants. On the one hand, it seems logical as the facial contour is the main focus of aesthetic implant restorations because the main goal is that the prosthetic rehabilitation will resemble a natural tooth. From a functional point of view, another soft tissue biological parameter that is important in periodontics is the attachment of gingival tissues around implants. On the other hand, controversy exists as to whether attached peri-implant tissues are strictly necessary for implant survival, and it is still a matter of debate because some successful cases lack sufficient keratinized tissue around implants. These two parameters, namely facial contour and keratinized tissues, have been the main topic of discussion in this field. However a third factor deserves special attention: vertical soft tissue thickness. To measure vertical soft tissue thickness, a buccal flap is raised after the crestal incision without elevating the lingual aspect. A periodontal probe is used on the bony ridge in the center of the planned implant placement to ensure direct measurement of crestal mucosal thickness. Vertical soft tissue thickness is a well-defined parameter that should not be confused with other soft tissue variables such as horizontal tissue thickness, soft tissue biotype or adherent gingiva. Differently from the classical measurements of keratinized tissue/attached gingiva, the vertical thickness of soft tissue is measured on the occlusal aspect of the alveolar ridge. Although it can be observed a close relationship, these are very different parameters. Vertical soft tissue height is gaining more and more attention as it is involved in the development of suprarestal tissue attachment around implants when they are exposed to the oral environment. The function of vertical peri-implant soft tissues as a unit is believed to be the protection of bone around the osseointegrated implant. It has been highlighted that the function of the peri-implant seal is "to maintain homeostasis of the internal environment in response to challenges from the external environment” (Lang et al. 1999). Due to the fact that the vertical thickness of soft tissues is a recently established parameter, there are no exact statistics on the prevalence of thin vertical tissues. By and large, it is estimated that 30% to 80% of patients may have thin tissue, although the exact variations in vertical tissue thickness have not been determined.

ASSOCIATION BETWEEN THIN SUPRACRESTAL TISSUE AND BONE RESORPTION:

In the relationship between vertical mucosal tissue thickness and crestal bone stability, it is suggested that if a minimum amount of vertical mucosal tissue is not available, bone loss may occur to ensure proper implant supracrestal attachment development to protect the implant from the oral environment. Therefore, it is necessary to understand how crestal bone may respond to different tissue thickness situations. The first mention of thin vertical tissue in the literature was a study by Abrahammson et al. (Abrahammson et al. 1997), which showed that implant sites with thin vertical tissue were prone to angular defects around implants after healing, whereas implant sites with thick mucosa were not associated with these defects. In parallel, early radiographic examinations showed that an implant-abutment junction positioned above the bone level caused crestal bone loss even before loading. This led to the hypothesis that any other factor was involved in bone resorption. In this regard, Davarpanah et al. (Davarpanah et al. 2000) and Holt et al. (Holt et al. 2002) proposed supracrestal implant positioning as a strategy to reduce bone resorption and achieve a better clinical relationship between crown and implant; Indeed, theoretically, this placement should reduce the influence of microgap and polished neck on crestal bone behavior. Based on this idea, test implants were placed supracrestally, control implants were placed at bone level, and implants were divided into groups based on initial vertical soft tissue thickness, allowing to investigate how crestal bone reacts to different vertical soft tissue sizes. The results showed that supracrestal implants in thin tissues had an additional 1.35 mm of bone loss during supracrestal attachment formation, while implants surrounded by thick tissues were almost free of bone loss, with only slight remodeling of 0.25 mm.

STH AND IMPLANTS WITH PS:

Later on, investigations were focused on understanding whether platform switching could nullify the effects of thin vertical tissues. A pilot study was conducted on patients with a thin vertical soft tissue biotype (Linkevicius et al. 2010). Two implants were placed next to each other, one with platform switching and one without. The implants were placed in a one-stage procedure, restored after 2 months and followed-up for 1 year. The result showed a bone loss of 1.81 mm around implants with a regular connection and 1.71 mm in implants with platform switching. This was the first study with clinical evidence explaining why bone is sometimes lost around implants with platform switching and a tapered connection. This study is often excluded from systematic reviews because the sample size was extremely small (i.e., 6 patients and 12 implants). Subsequently, Linkevicius et al. selected a 4.1-mm-diameter bone-level implant with at least 0.4 mm of platform switching for a follow-up study. The implant body and neck had parallel walls without coronal extension, and the abutment was 0.4 mm narrower than the implant body. Therefore, no additional compression was applied to the bone crest at the time of implant placement. In this study, 80 implants were placed in 80 patients. Half of the patients had 2 mm or less of vertical soft tissue (group 1) and half had more than 2 mm of vertical soft tissue (group 2). Tissue thickness was measured when the crestal incision was made and the buccal flap was raised, with the lingual flap left in place. Thickness was measured directly with a periodontal probe. Implants were placed using a one-stage (single-stage) approach and rehabilitated with screw-retained restorations. Radiographic examination was performed after implant placement, 2 months after healing, after restoration, and at 1-year follow-up. Results showed that implants in group 1 (thin tissue) had 0.76 mm mean bone loss after 2 months. At the 1-year follow-up, the average bone loss was 1.18 mm. Implants in group 2 (thick tissue) showed a mean bone loss of 0.17 mm 2 months after implant placement and 0.22 mm after 1 year of follow-up (Linkevicius et al. 2015). The differences between the groups were statistically significant ($P<0.001$) at both time points. This study demonstrated that platform-switching implants cannot prevent bone resorption if the tissues are thin. Interestingly, nearly 85% of implants in thick mucosal tissue showed no bone loss or loss of no more than 0.5 mm at 1-year follow-up. In contrast, nearly 70% of implants in thin soft tissue showed more than 1 mm of bone loss after 1-year follow-up. This

demonstrates the influence of soft tissue thickness on the degree of crestal bone remodeling. Based on this study, it can be concluded that platform switching does not prevent crestal bone loss if the crestal mucosal tissue is thin at the time of implant placement. In thick supracrestal soft tissue, the use of platform-switched implants maintained the crestal bone level with minimal remodeling. All implants used in the study were the same diameter (i.e., 4.1 mm), were placed in the same way (i.e., nonsubmerged), the same prosthetic approach and materials were used for the restoration (i.e., metal-ceramic, screw-retained), and patients were selected only if they met strict inclusion criteria. The only parameter that was different between the groups was vertical soft tissue thickness. Interestingly, the results of this study have been replicated by other groups. For example, a study by Vervaeke et al. (Vervaeke et al. 2014) showed that when using a longer Locator (Zest) abutment, which indicates thicker vertical tissues, less bone loss occurs after one year of service than shorter Locator abutments (no bone loss with a 4-mm abbutment; 0.38 mm bone loss with a 3 mm abutment; 0.86 mm bone loss with a 2 mm abutment; and 1.2 mm bone loss with a 1 mm abutment, indicating very thin tissues). Another study stated that there was no statistically significant difference between thin and thick tissue, but this study was designed differently and had a smaller sample size (Canullo et al. 2017). Hence, a systematic review combining all the data from these clinical trials was performed and concluded that there is sufficient evidence to conclude that implants placed in initially thinner vertical soft tissue have greater radiographic marginal bone loss in short-term follow-up (Suarez-Lopez et al. 2016).

POTENTIAL CAUSES OF BONE RESORPTION:

It is not completely understood why bone loss occurs when the tissue is less than 3 mm thick, although several hypotheses have been proposed. One of these is the plaque theory. It is suggested that intraoral bacteria and plaque should be at a certain distance from the bone level. If this distance is less than required, the bone resorbs to create sufficient distance for protection. The presence of bacteria is the cause of bone loss around implants in thin tissues during supracrestal attachment formation. When the implant is exposed to the oral environment through implant placement at one stage or upon implant discovery, a protective mechanism is activated. This is when bone loss occurs if the tissues are thin, which is why bone loss is seen as early as 2 months after healing screw connection. Support for this theory derived from the research of Waerhaug and Steen in 1952. They studied teeth extracted due to periodontal disease. They noted that no case showed calculus in direct contact with the bone; there was always some distance between bone and bacteria. This distance, called the “epithelial cuff”, extended 1.45 mm. Therefore, a similar explanation could also be given for implants, meaning the distance between bacteria and the crestal bone level. Supracrestal attachment formation begins when the implant is exposed to the oral environment. This exposure can occur with the placement of the healing screw or the permanent abutment, depending on what is attached to the implant. It is important to understand that if the implant is submerged, supracrestal attachment is not present; therefore, bone loss around submerged implants can be attributed to compression or contamination of the inner portion of the fixture. It has to be highlighted that supracrestal attachment formation begins when the implant is exposed to the oral environment. The substrate of development is the surface of the healing screw, prosthetic abutment, or temporary crown, depending on what has been connected to the implant. It has also been suggested that thin and thick tissues may have different blood supply, which may influence healing and subsequent bone loss in thin tissues. It has been hypothesized that when a flap is detached, blood supply is impaired, which leads to bone loss in thin tissues but has a limited effect in thick tissues, where more blood vessels are present. Nevertheless, at the present day, the mechanisms behind higher bone resorption in thin tissues need to be better clarified.

#STUDY 1:

Lops D, Stocchero M, Motta Jones J, Freni A, Palazzolo A, Romeo E. Five Degree Internal Conical Connection and Marginal Bone Stability around Subcrestal Implants: A Retrospective Analysis. Materials (Basel). 2020 Jul 13;13(14):3123. doi: 10.3390/ma13143123. PMID: 32668745; PMCID: PMC7411692.

Five Degree Internal Conical Connection and Marginal Bone Stability around Subcrestal Implants: A Retrospective Analysis

ABSTRACT: Background: There is limited information on the effect of the connection between subcrestally placed implants and abutments on marginal bone levels. The aim of the present retrospective study was to evaluate marginal bone levels after definitive prosthesis delivery around implants with an internal 5◦ conical connection placed in a subcrestal position. Materials and methods: Patients treated with fixed prostheses supported by implants placed at a subcrestal level between 2012 and 2018 were recalled for a follow-up examination. All implants had 5◦ internal conical connection with platform switching. Radiographic marginal bone level (MBL) was measured. MBL change between prosthetic delivery (t0) and follow-up examination (t1) was calculated. A multiple regression model was performed to identify the most significant predictors on MBL change. Results: Ninety-three patients and 410 implants, with a mean follow-up of 2.72 ± 1.31 years, were examined. Mean MBL was −1.09 ± 0.65 mm and −1.00 ± 0.37 mm at t0 and t1, respectively, with a mean bone remodeling of 0.09 ± 0.68 mm. An implant's vertical position in relation to the bone crest, the year of follow up and the presence of type-2 controlled diabetes were demonstrated to be influencing factors for MBL modifications. Conclusions: Subcrestally placed implants with platform switching and internal conical connection maintained stable bone levels over a mean follow-up of more than 2 years. How a tight internal conical connection between abutment and implant may contribute to this clinical evidence should be more deeply investigated. MBL variations seem to be mostly influenced by an implant's vertical position and presence of type-2 controlled diabetes.

#STUDY 2:

Lops D, Romeo E, Stocchero M, Palazzolo A, Manfredi B, Sbricoli L. Marginal Bone Maintenance and Different Prosthetic Emergence Angles: A 3-Year Retrospective Study. J Clin Med. 2022 Apr 4;11(7):2014. doi: 10.3390/jcm11072014. PMID: 35407622; PMCID: PMC8999635.

Marginal Bone Maintenance and Different Prosthetic Emergence Angles: A 3-Year Retrospective Study

Abstract: The aim of the present retrospective study was to assess marginal bone changes around implants restored with different prosthetic emergence profile angles. Patients were treated with implants supporting fixed dentures and were followed for 3 years. Marginal bone levels (MBL) measured at the prosthesis installation (t0) and at the 3-year follow-up visit (t1) were considered. The MBL change from t0 to t1 was investigated. Two groups were considered: Group 1 for restorations with an angle between implant axis and prosthetic emergence profile >30◦, and Group 2 for those with an angle ≤30◦, respectively. Moreover, peri-implant soft tissue parameters, such as the modified bleeding index (MBI) and plaque index (PI) were assessed. Seventy-four patients were included in the analysis and a total of 312 implants were examined. The mean EA in groups 1 and 2 was 45 ± 4 and 22 ± 7 degrees, respectively. The mean marginal bone level change (MBL change) of 0.06 ± 0.09 mm and 0.06 ± 0.10 mm were, respectively, in groups 1 and 2. The difference in the MBL change between the two groups was not statistically significant (p = 0.969). The MBL change does not seem to be influenced by the emergence angle for implants with a stable internal conical connection and platform-switching of the abutment diameter.

#STUDY 3:

Lops D, Romeo E, Calza S, Palazzolo A, Viviani L, Salgarello S, Buffoli B, Mensi M. Association between Peri-Implant Soft Tissue Health and Different Prosthetic Emergence Angles in Esthetic Areas: Digital Evaluation after 3 Years' Function. J Clin Med. 2022 Oct 23;11(21):6243. doi: 10.3390/jcm11216243. PMID: 36362471; PMCID: PMC9654584.

Association between Peri-Implant Soft Tissue Health and Different Prosthetic Emergence Angles in Esthetic Areas: Digital Evaluation after 3 Years' Function

Abstract: Background: The aim of the present retrospective study was to assess peri-implant soft tissue health for implants restored with different prosthetic emergence profile angles. Methods: Patients were treated with implants supporting fixed dentures and were followed for 3 years. Buccal emergence angle (EA) measured at 3 years of follow-up visits (t1) were calculated for two different groups: Group 1 (153 implants) for restorations with angle between implant axis and prosthetic emergence angle from ≥30◦, and Group 2 (67 implants) for those with angle ≤30◦, respectively. Image J software was used for the measurements. Moreover, peri-implant soft tissue parameters such as pocket probing depth (PPD), plaque index (PI) and gingival index (GI) were assessed, respectively. Results: A total of 57 patients were included in the analysis and a total of 220 implants were examined. Mean (±SD) EA in Groups 1 and 2 was 46.4 ± 12.2 and 24.5 ± 4.7 degrees, respectively. After 3 years of follow-up, a PPD difference of 0.062 mm (CI95% −0.041 mm; 0.164 mm) was calculated between the two groups and was not statistically significant (p = 0.238). Similar results were found for PI (OR = 0.78, CI95% 0.31; 1.98, p = 0.599). Furthermore, GI scores of 2 and 3 were found for nine implants (5.9%) in Group 1, and for five implants in Group 2 (7.5%). A non-significant difference (p = 0.76) was found. Conclusions: Peri-implant soft-tissue health does not seem to be influenced by EA itself, when a proper emergence profile is provided for implant-supported reconstructions in anterior areas.

#STUDY 4:

A. Palazzolo, V. De Giovanni, L. Proietto, D.Lops, E.Romeo Implant emergence angle on peri-implantitis: review of the literature and clinical case presentation. Dental Cadmos, 2023 Dec

Angolo di emergenza implantare e peri-implantite: revisione della letteratura e caso clinico

OBJECTIVES: The purpose of this study is to determine the role restorative emergence angle is associated with peri-implantitis. A narrative review of the literature was performed, and clinical case with 3-year follow-up was presented.

MATERIALS AND METHODS: A narrative review of the literature was performed using PubMed and Scopus databases, regarding emergency angles as risk factors for the occurrence of peri-implantitis. The literature search was performed by combining MeSH terms and free-text words combined through boolean operators (AND or OR). An example of the words used for the search process (PubMed) is listed below: "emergence angle OR emergence profile OR prosthetic contour AND peri-implantitis; implant emergence angle; emergence angle AND peri-implantitis". English-language studies published up to June 2022 were selected. Prospective studies of intervention, retrospective studies and case series with at least 10 patients were considered as eligible. All implant fixed prosthetic designs were evaluated namely: implant-supported single crowns, fixed partial restorations and full fixed prostheses. Human studies missing the inclusion criteria were excluded from this review. At the same time in vitro studies, animal studies, case reports, letters, conference abstract and narrative or systematic reviews were not considered.

RESULTS: Of the 264 total articles identified, after evaluation of titles and full text reading, duplicate articles and those having only the abstract were removed. After the screening process, 5 studies were included. The studies selected for review employed different methods for measuring implant emergence angle. Katafuchi and Yi measured EA radiographically from the mesiodistal aspect. The result was a higher prevalence of peri-implantitis if the EA value was >30°. Inoue et al. measured EA at mesial, distal, buccal, and lingual aspects. The result that emerged was that marginal bone loss tends to be less when the EA is comprised between 20°-40°. On the contrary, Lops et al. hypothesized that EA comprised

between 30-50 degrees might not affect peri-implant tissue health in the medium and long term follow up.

CONCLUSIONS: An emergence angle between 30° and 50° may not affect the stability of marginal bone-levels. The marginal bone-level evalua- tion, however, performed on the mesial and distal aspects of the implants, does not consider the vestibular and lingual/palatal aspects. In fact, this type of additional evaluation should require 3-D radiographs. More long-term prospective data are needed to confirm the findings of this review.

CLINICAL SIGNIFICANCE: Emergence angles between 30° and 50° in implants placed 1 mm below the bone crest might not be considered a risk factor for the occurrence of peri-implantitis.

#STUDY 5:

D.Lops, A. Palazzolo, L.Proietto, M.Mensi, S.Calza, E.Romeo Freehand versus static guided surgical technique for replacing single tooth edentulism by means of sub-crestally placed implants. A 3-year parallel randomized clinical study on marginal bone levels stability. Journal of Dentistry, Submitted

Freehand versus static guided surgical technique for replacing single tooth edentulism by means of sub-crestally placed implants. A 3-year parallel randomized clinical study on marginal bone levels stability.

Abstract

Objectives: The aim of the present prospective study was to investigate after a 3-year of follow-up any influence of the surgical technique, manual or digitally guided, on peri-implant marginal bone levels stability in implants placed 1 mm sub-crestally.

Materials and methods: Patients were treated by means of platform-switched implants provided with a 5 degrees internal conical connection and supporting single screw-retained fixed crowns. Marginal bone level (MBL) measured at prosthesis installation (t0) at 1 (t1), 2 (t2) and at 3 years of follow-up visit (t3) were considered. MBL change from t0 to t3 was investigated. Two groups were considered: Test Group (GD) for implant sites treated with a digitally guided surgery procedure. Control Group (FH) for implants surgically placed without digitally guided surgery, respectively. Additionally, for both groups MBL changes were correlated to different supra-crestal soft tissue height (STH) amounts: less than 3 and ≥ 3 millimeters, respectively.

Results: 60 implants were examined. MBL change difference between the two groups was 0.11 ± 0.22 mm and such value was not statistically different (p=0.61). Variation of MBL with different STH values in relation to time (t0, t1, t2, t3) was also investigated: at time of prosthetic loading the mean MBL for implants with STH less than 3mm was 0.33mm higher than implants with STH ≥ 3mm; such value was close to statistically significant (P=0.065).

Conclusions: the digitally guided implant placement does not prevent marginal bone remodeling itself, if compared to a manual procedure performed by an experienced operator. Early MBL may be influenced by the STH amount in a sub-crestally placed implants with an internal conical

connection and platform switching of the abutment diameter.

Clinical significance: The amount of STH could influence the early MBL in implants placed below the ridge with an internal conical connection and platform change of the abutment diameter.

This study represents the core project of this thesis. Accordingly, the clinical protocol and results will be discussed in extenso

METHODS AND MATERIALS:

This parallel-group randomized controlled clinical trial was conducted at the Department of fixed and implant prosthodontics directed by Prof. Eugenio Romeo, Dental Clinic, University of Milan. Patients were recruited, treated and followed-up between 2018 and 2023. This study was performed in full accordance with the Declaration of Helsinki on experimentation involving human subjects. Subject participation in this study was on a voluntary basis and all of the eligible patients received comprehensive written and verbal information and signed informed consent forms before their enrolment. Before commencement, the present investigation received the approval by the Ethics Committee of the University of Milan (Prot. No. EC 1564/18). This study was retrospectively recorded in a public registry of clinical trials (www.clinicaltrials.gov/ NCT06250621). The null hypotesis of this study was that no differences can be expected in terms of marginal bone levels between dental implants placed by static computer-guided surgery or freehand. The primary enpoint of this study was to analyze marginal bone levels up to 3 years after definitive prosthesis delivery. The following endpoints were considered as secondary outcomes of this investigation: peri-implant probing pocket depth (PPD), modified bleeding index (mBI), modified plaque index (mPI), supracrestal tissue height (STH), implant success rate, surgical and prosthetic complications.

GENERAL FEATURES OF THE STUDY:

Patients requiring single or multiple implant-supported rehabilitations were consecutively enrolled at the Department of fixed and implant prosthodontics of the University of Milan. Inclusion and exclusion criteria are reported in Figure 7. All patients underwent the same procedures and received one or more dental implants by static computer-guided implant surgery (Test group, GD) or freehand implant positioning (Control group, FH). The same implant system and typology was used (Anyridge, MegaGen Implant Co., Gyeongbuk, South Korea). According to the manufacturers' instruction, implant fixtures were positioned 1 mm subcrestally at the time of implant placement. A general overview of the dental implant is depicted in Figures 8 & 9.

INCLUSION CRITERIA		EXCLUSION CRITERIA	
GENERAL	LOCAL	SYSTEMIC	LOCAL
Age comprised between 18 and 90 years	No needing of bone regeneration	Blood disorders (e.g. leukocyte disfunction, hemophilia, malignant chronic diseases, etc…)	Untreated/ Uncontrolled periodontitis
Single or multiple tooth loss (partial edentulism)	Pristine bone of at least 6 mm in width (minimum residual bone of 1 mm both buccally and lingually) and 10.5 mm in height	Prolonged steroid therapy/ Uncontrolled endocrine disorders	Recurrent oral infections
Willingness/ Capability to attend all time points	Presence of opposite natural or prosthetic tooth at the level of the antagonistic arch	Bone/Renal/Liver metabolic disorders/ Severely immunocompromised patients	Mucosal disorders (e.g. lichen planus)/ Benign or Malignant Oral lesions
		Previous chemotherapy and/ or radiotherapy of the craniofacial region	Inadequate oral hygiene/Poor compliance/Full mouth plaque score (FMPS) and Full mouth bleeding score (FMBS) >20%
		Current Pregrancy/ Breastfeeding	Oral Parafunctions (e.g. bruxism, diurnal parafunctions, clenching, grinding)
		Alcohol/Drug abuse	
		Current smokers (>10 cigarettes/ day)/pipe/cigar	

Figure 7: Inclusion and Exclusion criteria

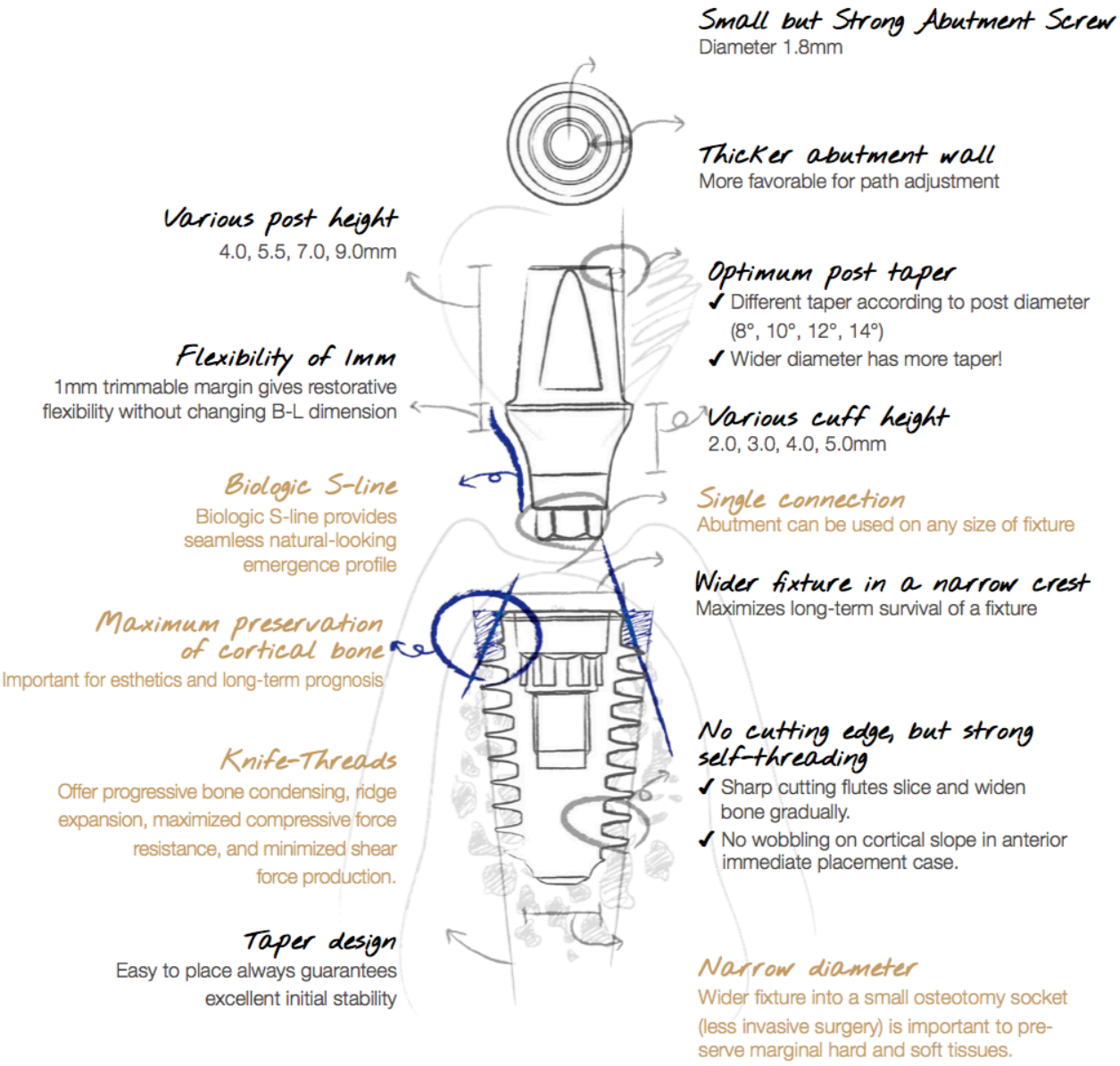


Figure 8: Details of the implant system and typology; macrostructural and microstructural features. The fixture-abutment interface is characterized by an internal conical connection which measures 2.8 mm with 5° hexagonal indexing;

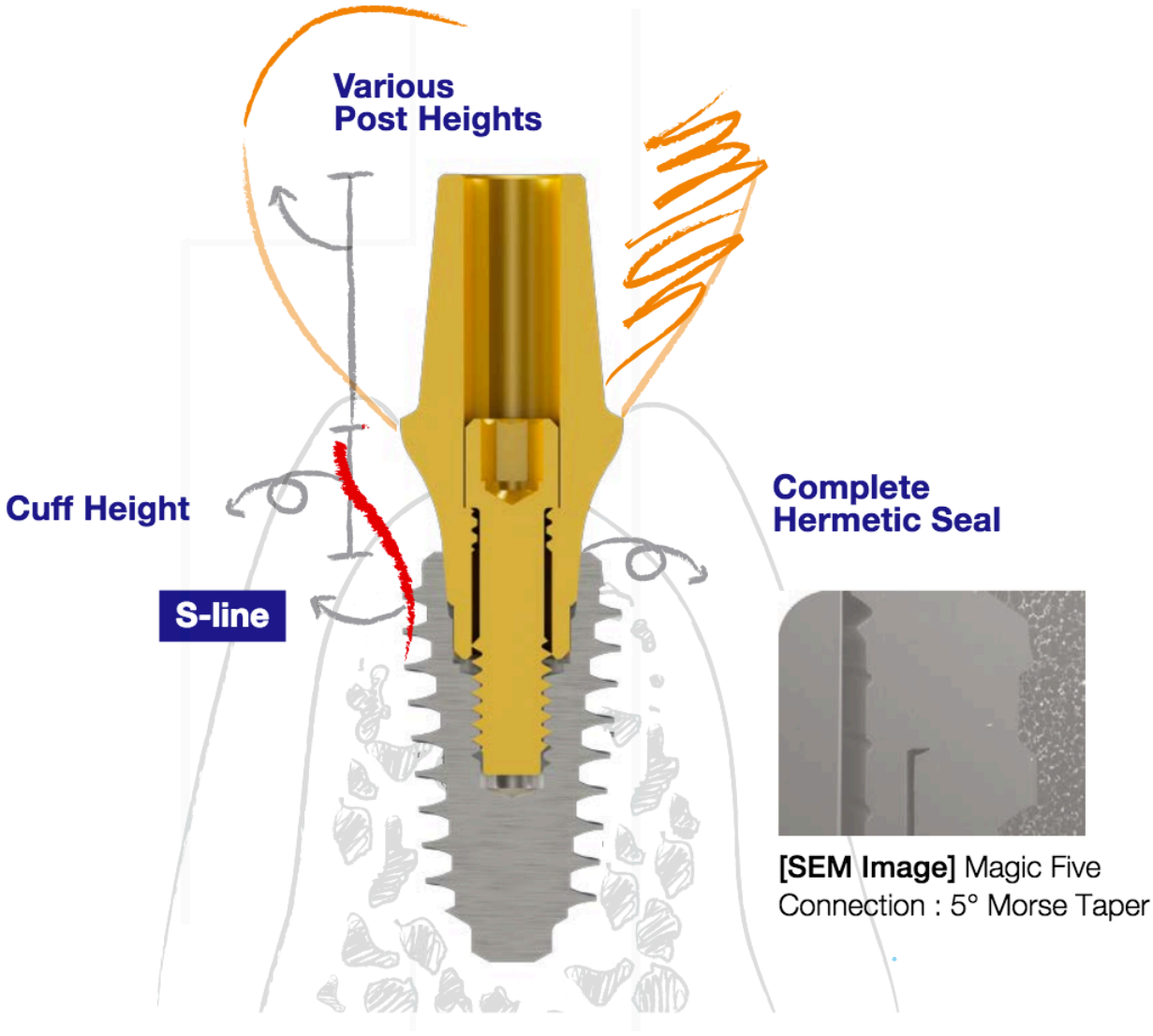


Figure 9: Features of the implant-abutment interface: reduced prosthetic microgap, platform away from the bone margin, reduced unscrewing/rotation of the prosthetic components

SAMPLE SIZE CALCULATION:

The sample size of this study was calculated via Monte-Carlo simulation (B=1000) assuming a hierarchical model with implants nested within patients. Outcome was simulated from a Gaussian distribution with residual standard deviation of 0.35 mm. The main effect of interest was the differential MBL variation from baseline to one year in the two groups (time*group interaction term) and was assumed to be of at least 0.45 mm. The simulated model assumed a single random term (standard deviation intercept = 0.3). The number of implants within patient was simulated using a zero- truncated Poisson distribution (approximately 1 to 8 implants per patient range). A total of 60 implants allowed a power of at least 95% at a 5% significance level.

RANDOMIZATION:

An independent investigator, not involved in treatment of patients, prepared a computer- generated randomization list using a balanced, randomly permuted block algorithm, assigning the two implants of each patient to the different groups (Guided Surgery: Test; Freehand: Control). Randomization codes were enclosed in numbered, identical, sealed, opaque envelopes, thus guaranteeing the allocation concealment. Digital surgical planning and surgical templates were carried out for all recruited patients. The day of the surgery, after randomization disclosure (envelope opening), a different operator was selected based on the treatment assignment. A non-expert doctor (less than 20 implants placed in the professional activity) was selected for the procedures related to the GD Group (Test); a skilled operator (more than 1000 implants placed in the professional activity) was selected for the procedures related to the FH Group (Control), respectively. Treatment allocation was concealed to the operators in charge of executing the surgical procedures until the time of the start of the intervention.

INVESTIGATED OUTCOMES:

- Soft tissue height (STH) at the time of flap detachment
- Marginal bone Levels (MBL) obtained by standardized x-rays at baseline and each year annually up to 3 years
- Peri-implant pocket probing depth (PPD) measured by a calibrated plastic probe (TPS probe, Vivadent, Schaan, Liechtenstein) at 4 sites per implant namely: mesially, distally, buccally, lingually/palatally
- Modified sulcus bleeding index (mBI) (score range: 0-3) evaluated by "walking probing" through the mucosal margin and within 30 seconds
- Modified Plaque index (mPI) (score range: 0-3) evaluated by "walking probing" through the mucosal margin
- Prosthetic- and implant-related complications from baseline (final prosthesis delivery) and up to 3 years of observation

FLOWCHART:

A brief graphic summary of the appointments and procedures performed over the course of this clinical study is depicted in Figure 10 (Flowchart) and Figure 11 (Experimental Timeline).

Tasks	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
	Screening Visit	Oral hygiene	Folllow-up and Documen tation	Implant placement	1-2 Weeks FU (after implant placement)	Prosthetic impression	Provisional Restoration	Final Restoration (up to 6 months after implant placement)	1year FU (after final restoration)	2 years FU (after final restoration)	3 years FU (after final restoration)
		<14 Days	<7 Days	Time 0	7-14 Days	12 Weeks	14 Weeks	20 Weeks	12 months	24 months	36 months
Informed Consent(Pregnancy	X										
Inclusion/Exclusion Criteria	X			X							
Medical & Dental History	X										
Demographics	X										
PPD, BOP, PI			X					X	X	X	X
Bone quality				X							
Height of keratinized gingiva	X							X	X	X	X
CBCT SCAN		X									
Intraoral Radiographs	X			X			X	X	X	X	X
Intra-Oral Photographs	X		X	X	X	X	X	X	X	X	X
Suture Removal					X						
Wound healing assessment											
Implant Placement				X							
Permanent Prosthesis Placement								X			
Spectrophotometric measurements								X			
Fixture impression						X		X			
Implant Survival and Success								X	X	X	X
Adverse Event		X	X	X	X	X	X	X	X	X	X

Figure 10: Flowchart of the experimental protocol

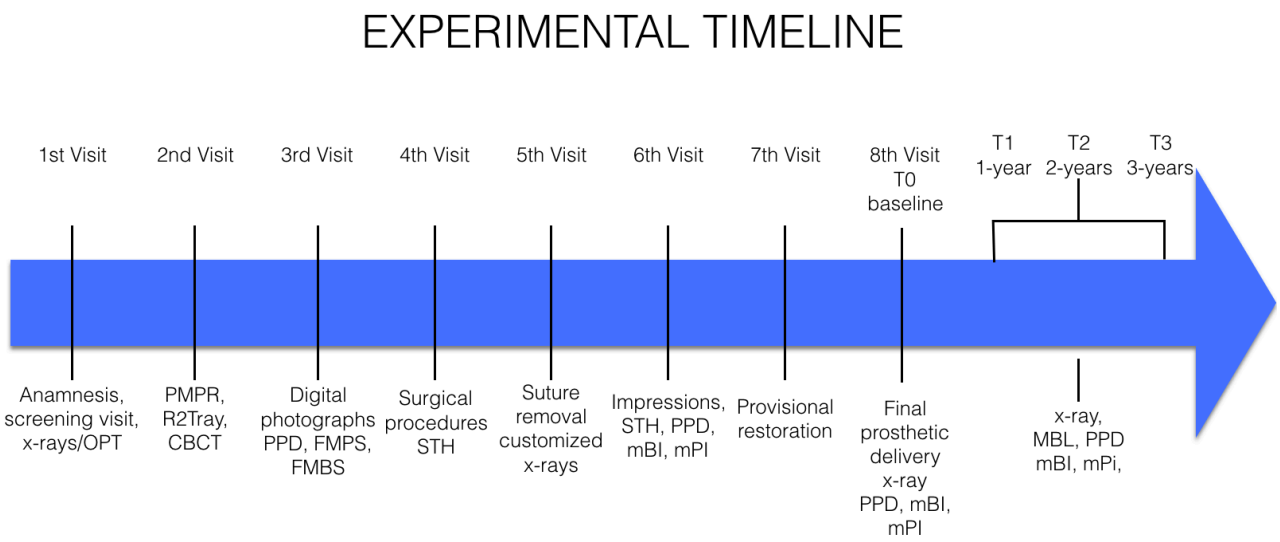


Figure 11: Experimental Timeline

1° VISIT:
During the first appointment, the medical history of each patient was obtained. Then, a general inspection of the oral cavity was performed and several aspects were investigated such as: type of edentulism (e.g. upper or lower arch, single or multiple, etc…), presence of decayed teeth, signs of gingival inflammation and presece of previous rehabilitations. All these items were noted in a specifically-designed form. History of undiagnosed/treated periodontitis was investigated. In the event that this screening phase had revealed potential site fulfilling inclusion/exclusion criteria, radiographic (x-rays and ortophantomography) and photographic examinations were carried-out.

2° VISIT:

Professional mechanical plaque removal (PMPR) and hygiene instructions were provided. Then, in order to produce surgical templates, radiological 3D examination was performed according to the manufacturers' instructions; In accordance with R2Gate guided planning procedures (Megagen Implant, Seoul, South Korea®), polyether impressions of both arches were made so as to obtain a master model. A second polyether impression was taken by a special holder (R2Tray holder, Figure 12). Hence 3D radiological examination (CBCT) was performed with the R2Tray in place, supported by the remaining teeth. Due to the technical specifications of the R2Gate system, CBCT files were converted to multiframe DICOM and were used and analyzed for CAD/CAM design (Figure 13). Cast models were digitized by extraoral scanner (EOS) of both arches, thus obtaining a precise acquisition of the STL file, and the position in maximum intercuspation. Moreover, the scanning of the surface of the support inserted on the plaster model (EOS) was obtained. The laboratory performed a series of scans using EOS: scanning of the single arches, the arches in occlusion, the single model (inner and outer surface), and the plaster model with the R2Tray spoon inserted. Based on the matching between the file obtained from the extraoral scan, with the volumetric information from the CBCT, using R2 Gate system, the implant surgery was planned and a radiological template was made by CAD/CAM methods. The entire process is summarized in Figure 14.



Figure 12: R2Tray holder

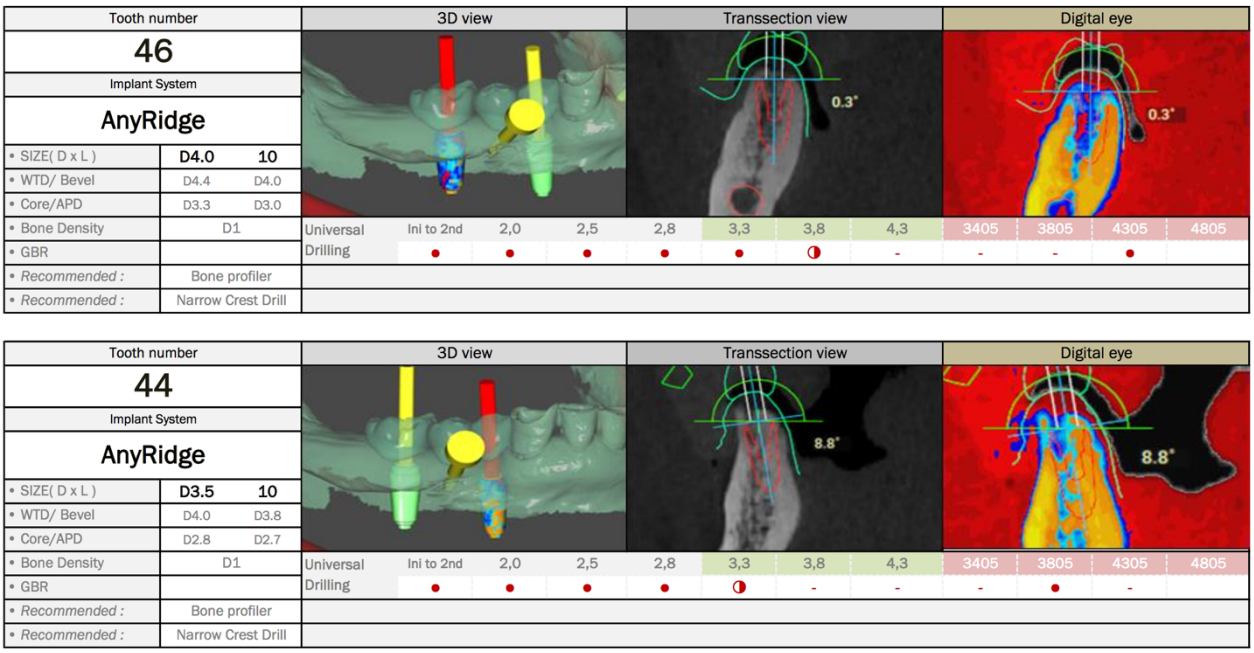


Figure 13: Digital planning through R2Gate software; details related to: tooth position, implant diameter, implant height, bone density. Indications on drilling protocol are provided.

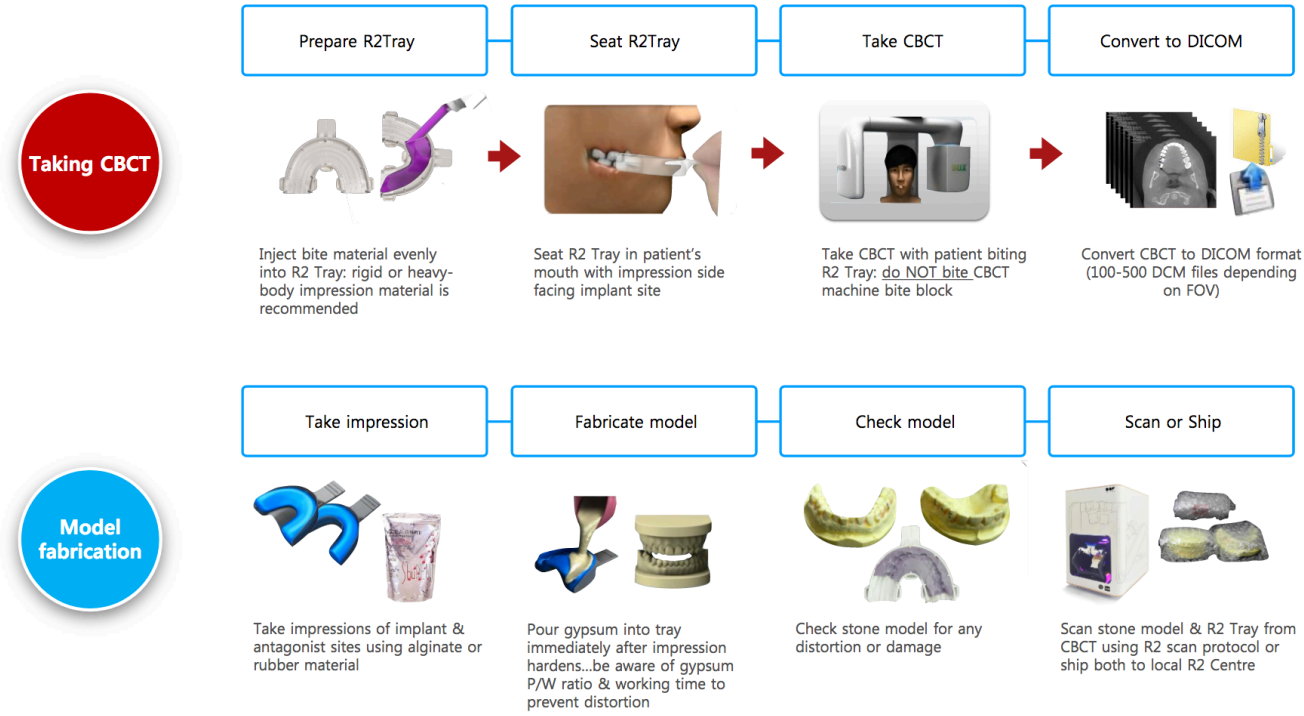


Figure 14: Graphic flowchart showing each step in order to obtain CAD/CAM surgical templates

3° VISIT:

At the 3rd appointment digital photographs and periodontal parameters were collected (e.g. periodontal charting, PPD, FMPS, FMBS).

4° VISIT:

During the 4th appointment, surgical procedures were performed. After obtaining signed consent form, envelope opening led to group assignment: implant assigned to test group were treated by one non-experienced operator through static computer-guided implant surgery (Figure 15); implant assigned to control group were placed freehand by one experienced operator. During surgery, after buccal full-thickness flap elevation, soft tissue height (STH) was assessed by means of a periodontal probe. The probe was positioned in an upright position, using the center of the future implant placement at the bony crest level as reference point. Measurements were rounded up to 0.5 mm. Implant size, intraoperative complications and achieved primary stability were obtained. The entire surgical protocol is carefully decribed in a specific section below.

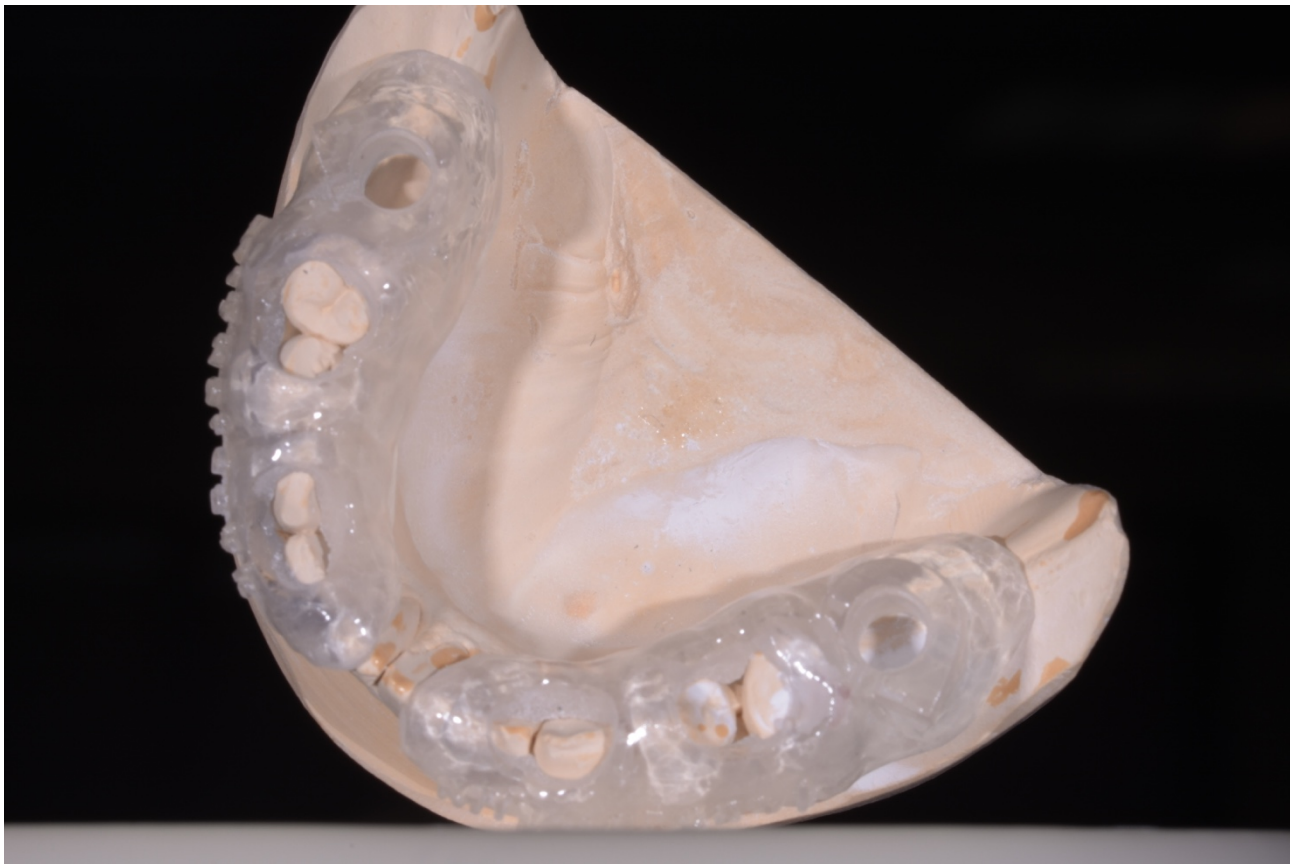


Figure 15: Features of the tooth-supported surgical templates.

5° VISIT:

7-14 days after surgical intervention, suture removal and x-ray of the recipient site were obtained. Radiographs acquisition was performed with customized x-ray holders in order to guarantee the same projection in the same patient at different checkpoints, in order to reduce distortion. Customization was made through silicone material, so as to impression the x-ray holder and the neighboring teeth in a well-defined position (Figure 16).



Figure 16: Customized x-ray holder, from Lops et al. 2013

6°VISIT:

12 weeks after implant positioning, impressions were taken with polyether material by a pick-up system. Soft tissue height (STH) was measured after flap elevation. A healing abutment was screwed upon the fixture and the flap was closed through single interrupted sutures. Peri-implant probing pocket depth (PPD), modified plaque index (mPI), modified sulcus bleeding index (mBI) and occurrence of adverse events at the site of surgery were recorded.

7°VISIT:

2 weeks after implant uncovering (14 weeks after implant placement), provisional restorations were applied.

8°VISIT:

5 months after implant placement (20 weeks), definitive prosthetic rehabilitations were delivered. The entire prosthetic protocol is carefully described in a specific section below. Peri-implant related biometric parameters were recorded (PPD, mBI, mPI) and customized radiographs were performed as baseline timepoint (T0) 2 weeks after loading the final prosthesis.

FOLLOW-UP VISITS:

From baseline (T0), patients underwent professional mechanical plaque removal (PMPR) according to their risk profile. Patients were visited each year annually and up to 3 years (1 year after loading, T1; 2 years after loading, T2; 3 years after loading, T3). The following parameters were recorded: PPD, mBI, mPI. Dental radiographs through standardized projection were performed to investigate marginal bone levels (MBL). An illustrative case study showing the radiographic progression over time is reported from Figure 17 to Figure 23. Any adverse event related to dental implants or rehabilitations was annotated at each timepoint.



Figure 17: Pre-operative x-ray



Figure 18: X-ray at implant placement

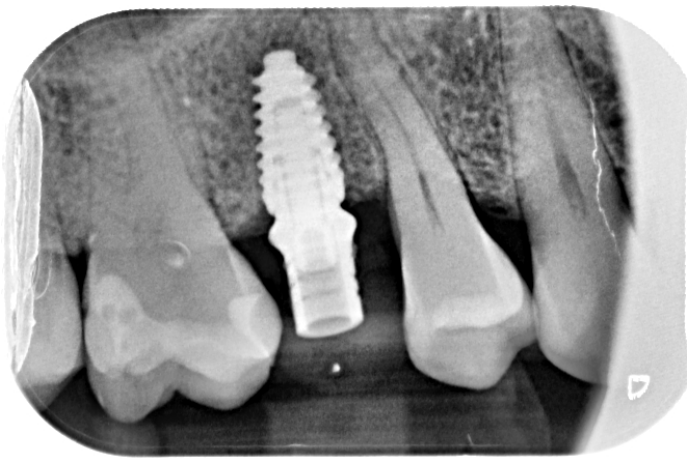


Figure 19: X-ray of the provisional restoration

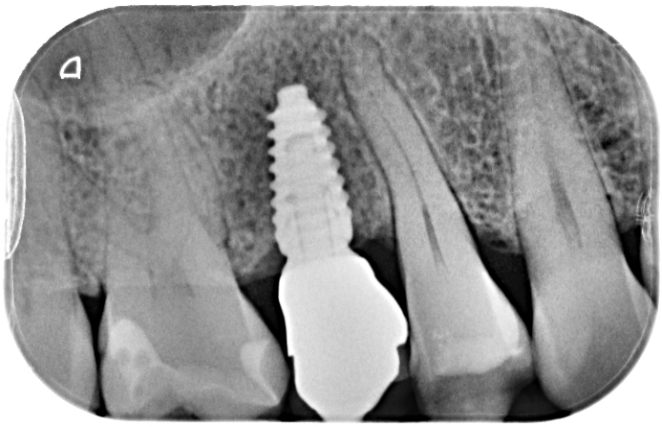


Figure 20: X-ray at baseline (T0)

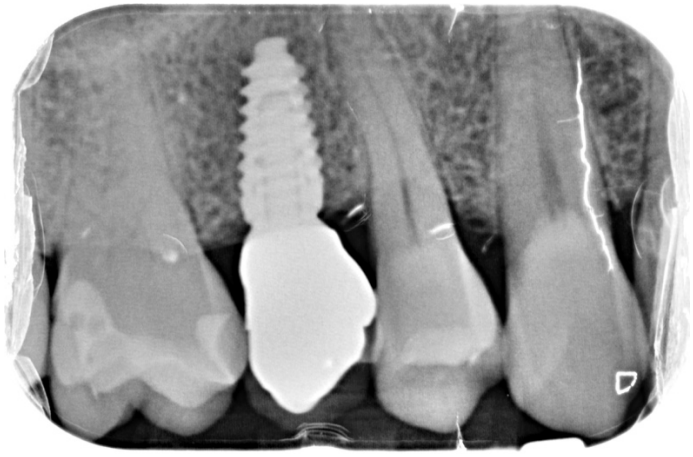


Figure 21: X-ray after 1 year (T1)

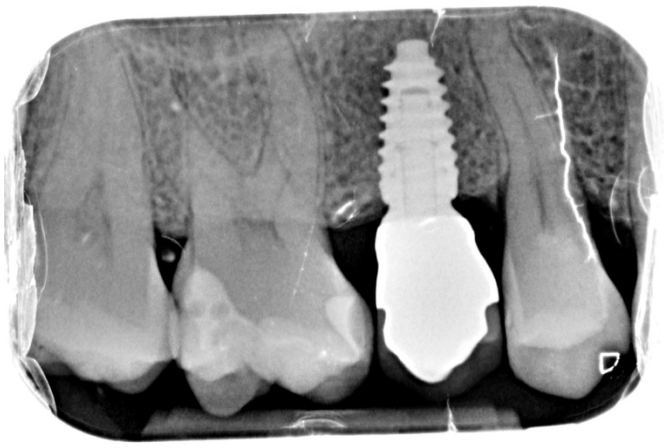


Figure 22: X-ray after 2 years (T2)

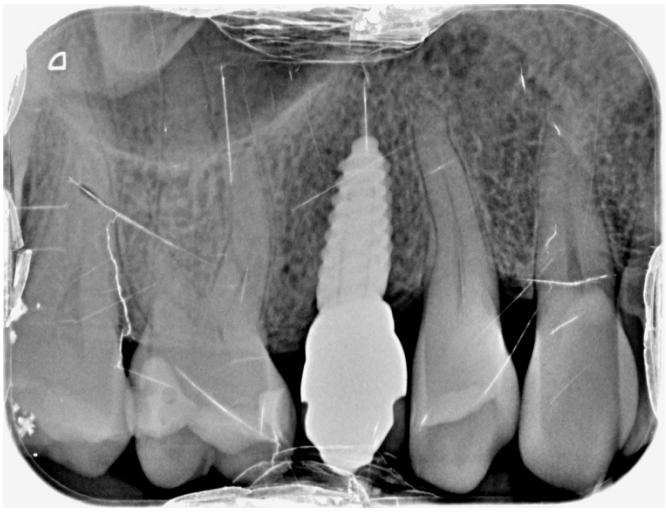


Figure 23: X-ray after 3 years (T3)

RADIOGRAPHIC ANALYSIS:

The software ImageJ (Image J, National Institute of Health, Bethesda, Rockville, MA, USA) was used for radiographic assessment. It allows image measurement and can be applied to most of the common and important image formats in biomedical imaging. It can also acquire images directly from scanners, cameras, camcorders, or other video sources.

In this RCT, radiographic images were imprinted on phosphor plates measuring 22x35 mm and 31x41 mm. Radiographs were acquired by digital method via VistaScan Mini View scanner (DÜRR DENTAL SE, Bietigheim-Bissingen, Germany), combined with analysis and saving by digital program VistaSoft (version 2.4.10) (DÜRR DENTAL SE, Bietigheim-Bissingen, Germany). Radiographs were downloaded, sorted by patient and follow-up period, then assessed using ImageJ software (National institute of Health, Bethesda, Rockville, Maryland, USA) by a calibrated single operator. Measurements were rounded to the nearest hundredth of a millimeter, rounding up if the last digit was greater than or equal to 5. Before measuring MBL, each radiograph was calibrated using the diameter and length of the implant as reference measurements to correct for any distortion (Figure 24). Mesial and distal measurements were performed, then a mean value was recorded. MBL was calculated as the distance between the implant neck and the first detectable bone to implant contact or the distance between the implant neck and the marginal

bone in contact with the line drawn by the implant shoulder following the long axis of the implant (Figure 25). A positive value was assigned to the measurement in case the bone contact was apical to the implant neck. When the bone margin was coronal to the implant neck, a negative value was recorded.

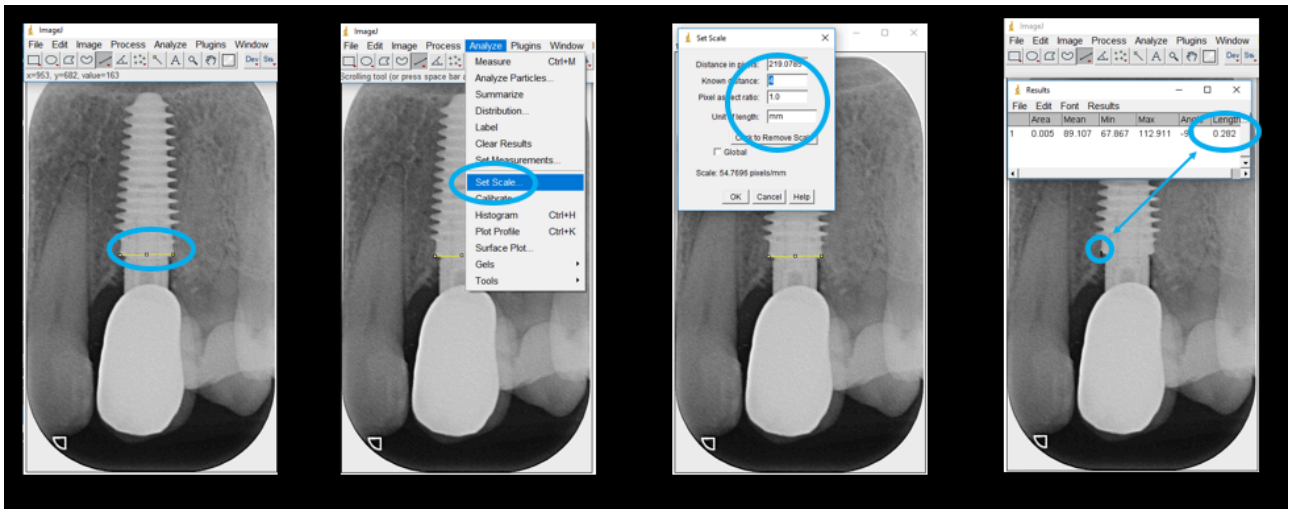


Figure 24: Process to set a scale using known measures (e.g. diameter and height) as references to calibrate each radiograph

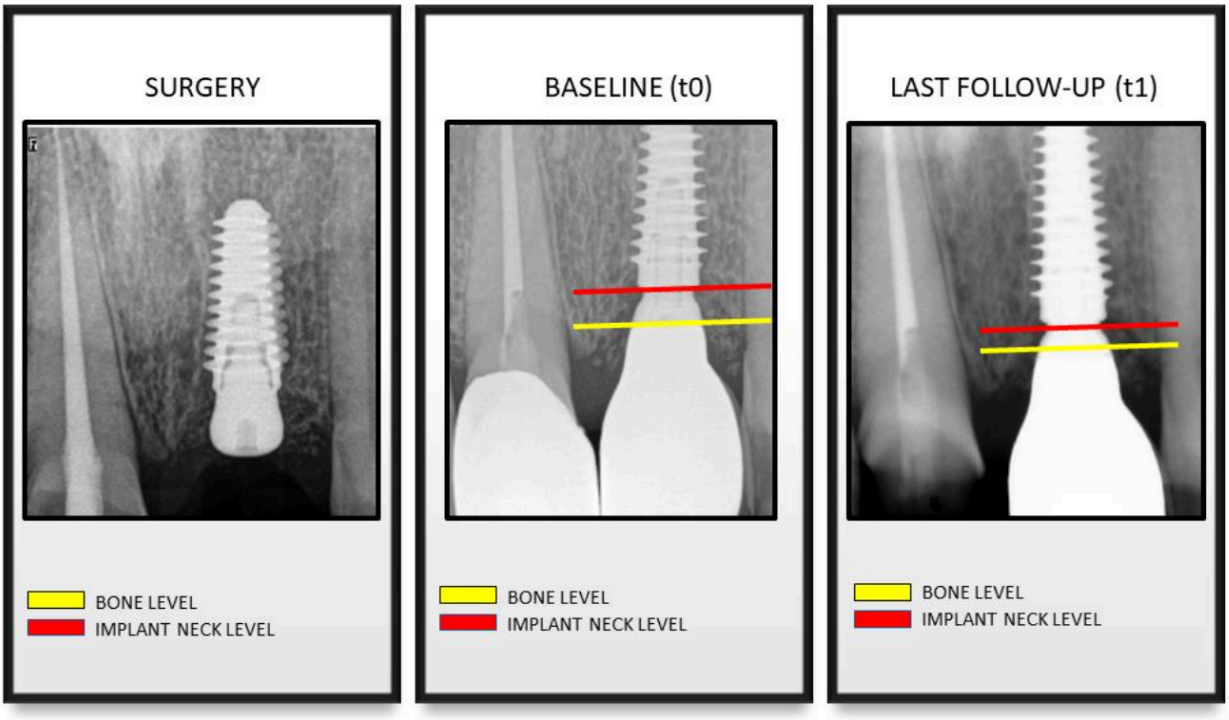


Figure 25: MBL measurements were taken at the mesial and distal aspect of each implant.

SURGICAL PROTOCOL :

Before treatment, patients were clinically and radiographically evaluated. Panoramic and x-rays with apico-peri-apical projection were used as a first level exam to evaluate the bone quantity before implant placement. A second level exam cone beam TC (CBCT) was also performed in order to evaluate the correct and prosthetically guided implant placement. For each implant planned, the STL digital file was obtained in order to provide a tooth retained template for a surgically guided placement (Figures 26 and 27). R2Gate digital workflow was used to provide from digital planning to the surgical template for the guided implant placement. (FIG.2) for a guided surgery approach (GD Group) (Figure 28) or with a standard free-hand surgical approach without any additional device (FH Group) (Figure 29).

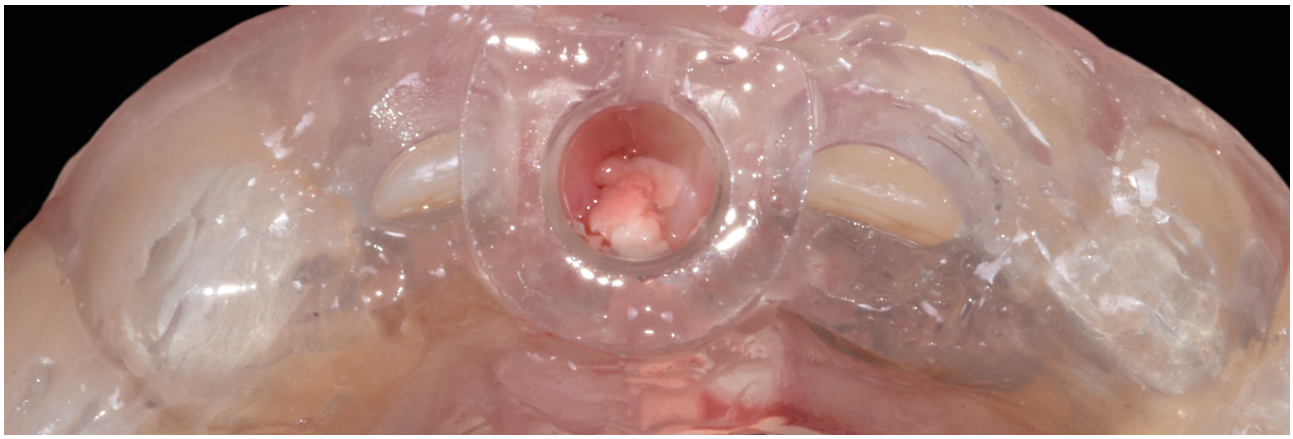


Figure 26: Clinical picture showing the drilling procedure through the tooth-supported template, occlusal view.

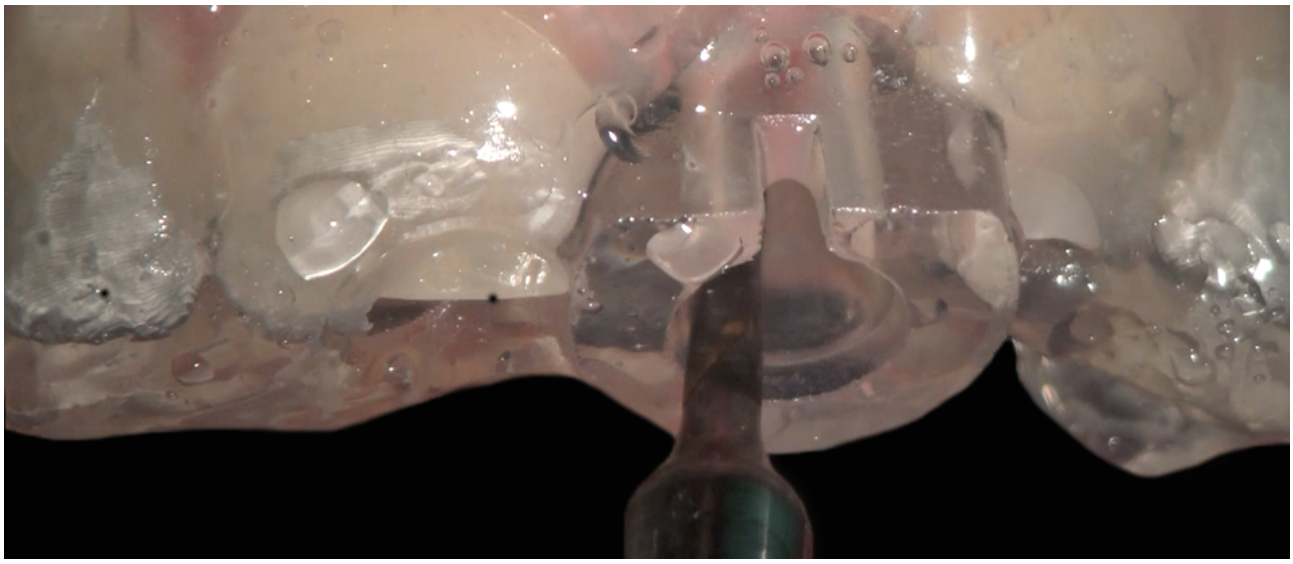


Figure 27: Clinical picture showing the drilling procedure through the tooth-supported template, vestibular view.



Figure 28: Illustrative case showing implant insertion by static computer-guided surgery, Test Group.

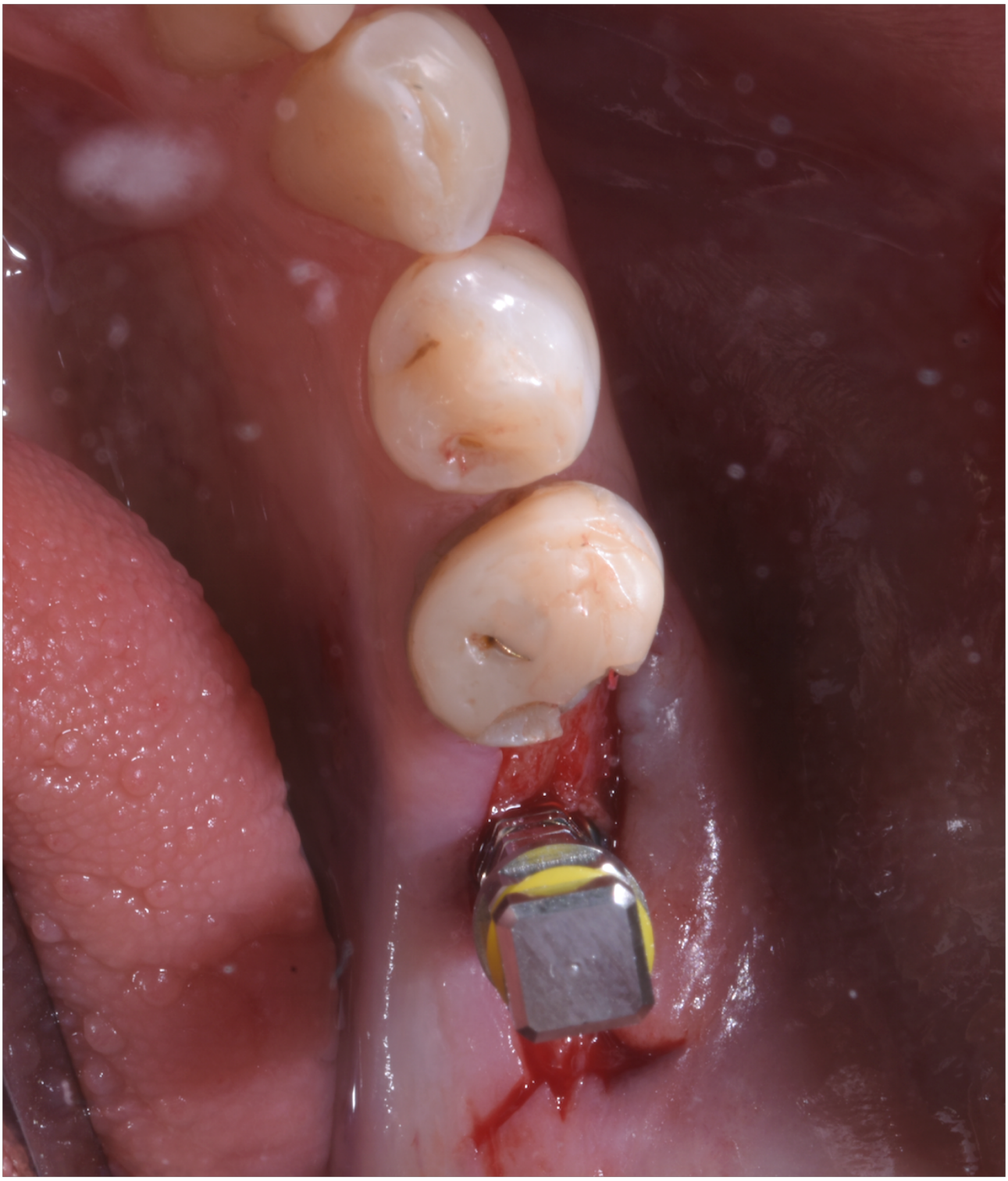


Figure 29: Illustrative case showing freehand implant placement, Control Group.

A two-stage surgical technique was chosen. Implants were placed (Anyridge, Megagen Implants, Seoul, Korea) 1 mm below the crestal level, as recommended by the manufacturer.

After flap elevation the height of the supra-crestal soft tissue (STH) was measured by means of a calibrated probe.

An inter-implant distance of 3 mm at least, and/or an interproximal space from 1.5 to 3 mm between an implant and the adjacent tooth were observed. Flaps were sutured over the implants to allow a submerged healing. Antibiotics were prescribed for 5 days (amoxicillin/clavulanate 1 g twice a day) and ibuprofen 600 mg when needed. Surgical re- entry was performed three months after the implant placement and trans-mucosal healing abutments were installed.

PROSTHETIC PROTOCOL:

Two weeks after surgical re-entry, an implant-level impression was taken to provide for screw- retained temporary restorations. Prostheses were inserted from one to six weeks after implant level impression. After a period of 8 to 12 weeks for peri-implant soft tissue conditioning, definitive implant level impression was taken.

Only fixed, screw-retained single crowns (SC) were employed to restore patient edentulisms. All restoration were fabricated by the same dental technician. They were made of zirconia and cemented on implant abutments provided by the manufacturer. Implants were placed in the posterior jaw region and in both dental arches, spanning from the second premolar to the second molar.

In order to avoid any interference of the prosthetic design on peri-implant tissue stability specific emergence profile shapes (Figure 30) were provided for the crowns manufacturing a convex esthetic profile to support the gingival margin, establishing the cervical morphology of the implant crown itself;



Figure 30: Details of the emergence profile.

a concave boundary profile apical to the esthetic one and in direct contact with the peri-implant junctional epithelium tissue; a straight profile immediately coronal to the implant platform and in direct contact with the peri-implant connective tissue (Figure 31).

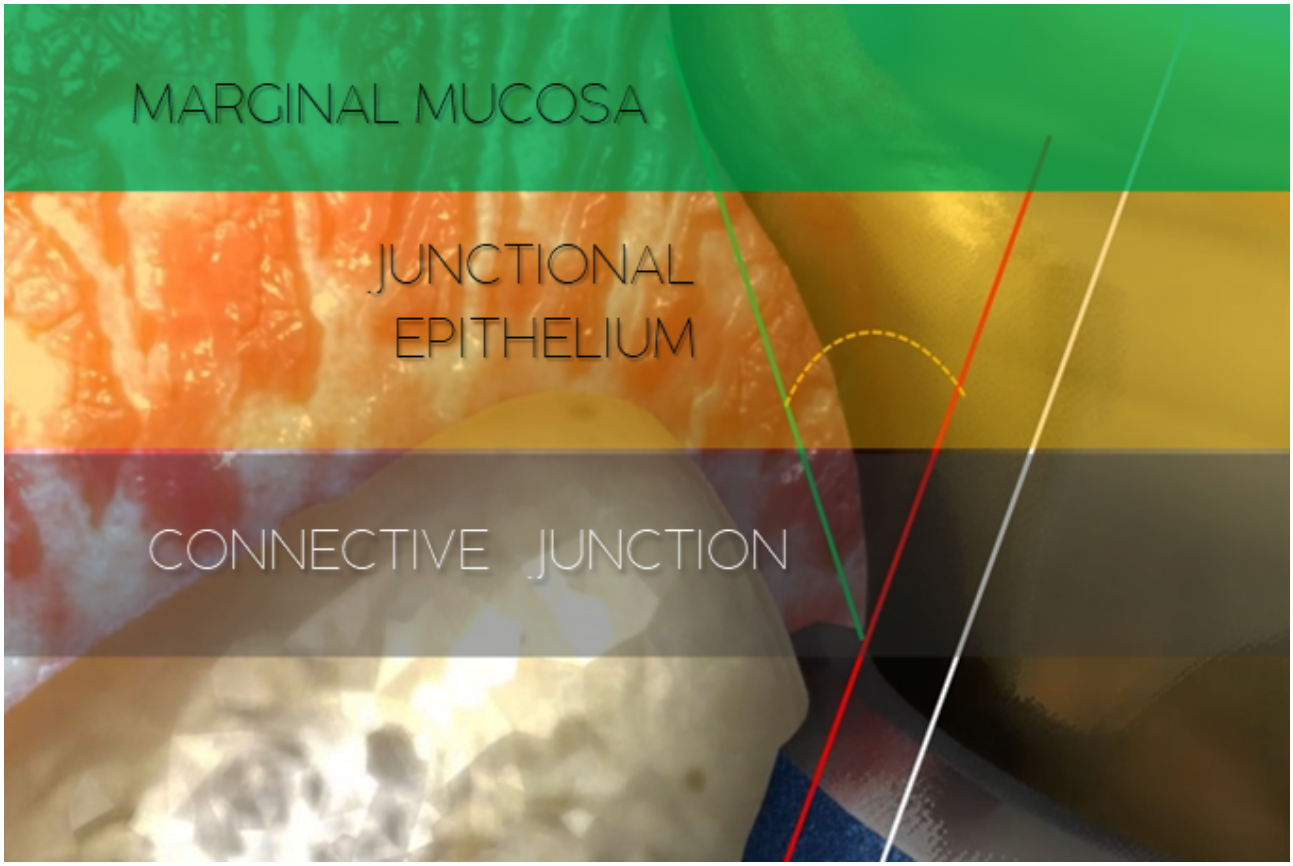


Figure 31: Characteristics of the emergence profile in relation to the Implant supracrestal attachment.

Moreover, emergence angles (EA) were chosen for all the definitive restorations included (Figure 32). An interproximal EA ≤30° and a buccal EA between 30° and 45° were digitally planned (Figure 33) by means of a dedicated CAD software (Exocad, Darmstadt Germany).

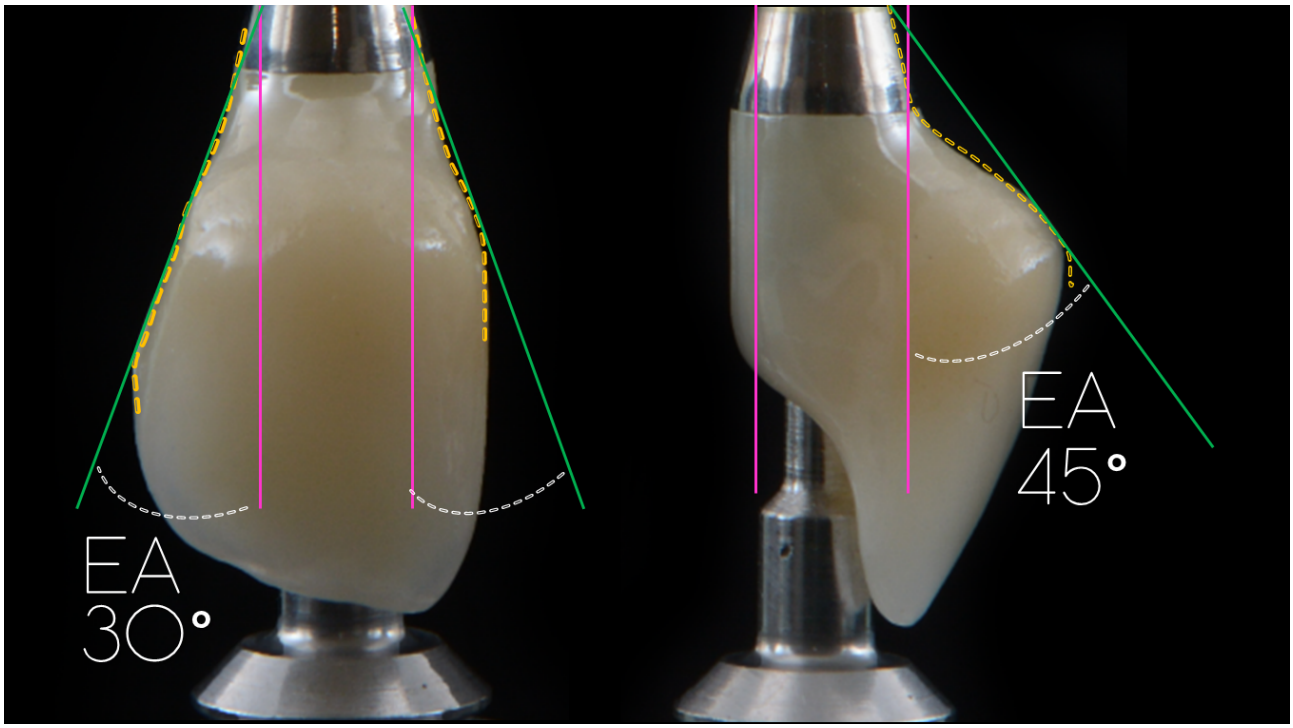


Figure 32: Details of vestibular and interproximal emergence angles

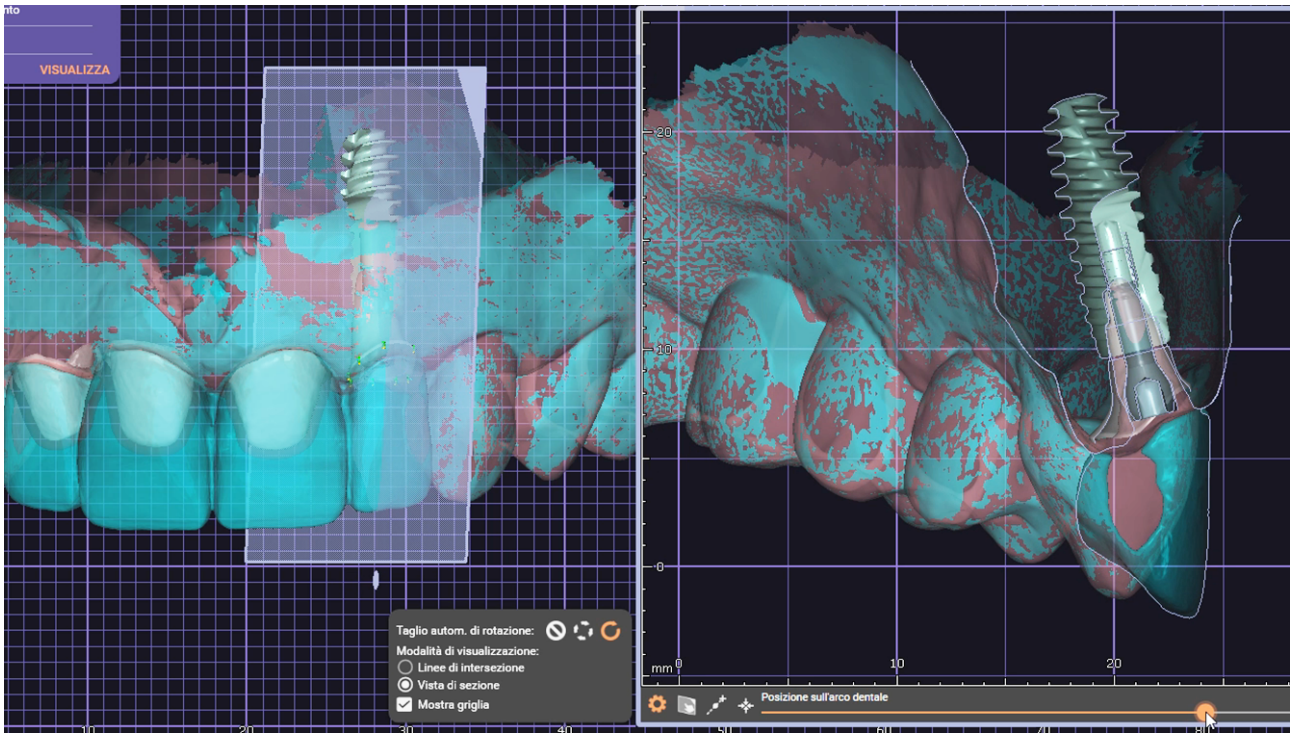


Figure 33: Digital planning of the emergence angle (EA) and profile (EP)

All the restorations were screw-retained with a torque of 25 N/cm by means of a proper torque wrench. After 2 weeks of loading, patients were recalled and an intraoral periapical radiograph of the restored implant site was taken; also, peri-implant clinical parameters were assessed.

STATISTICAL ANALYSIS:

Data were analised considering implant as statistical unit. Data were described using mean and standard deviation for quantitative variables and counts and percentages for categorical variables. Given the hierarchical structure of the data (i.e., Implants nested within patients), data were modelled using Generalised Linear Mixed Models (GLMM) with a Gaussian family for PPD and MBL, and a Poisson distribution for BOP and PI, expressed as counts within patient. Results are reported as estimates (difference for Gaussian models, rates for Poisson models) and corresponding 95% confidence intervals. All tests assumed a 5% two-sided significance level. All analyses were performed using R (version 4.3.2, R Core Team).

RESULTS:

Eighteen patients (8 males and 10 females, respectively) aged from 22 to 84 years (mean age 55.6±32.4 years) were recruited in the present study, treated with 60 implants and consecutively followed in a 3 years period from the definitive prosthesis installation, were included in the present study.

Implants features by different sizes are reported in Tables 1 and 2, respectively. Sixty (60) implant-supported screw-retained single crowns were analyzed.

Table 1. Frequency of implant length in GD Group (Guided surgery) and FH Group (free-hand).

		GD	FH	Total
Implant Length (mm)	7	1 (3%)	1 (3%)	2 (3%)
	8.5	5 (17%)	5 (17%)	10 (17%)
	10	16 (53%)	16 (53%)	32 (53%)
	11.5	8 (27%)	6 (20%)	14 (23%)
	13	0 (0%)	2 (7%)	2 (3%)
Total		30	30	60

Table 2. Frequency of implant diameter GD Group (Guided surgery) and FH Group (free-hand).

		GD	FH	Total
Implant Diameter (mm)	3.5	0 (0%)	6 (20%)	6 (10%)
	4.0	29 (97%)	23 (77%)	52 (87%)
	4.5	1 (3%)	1 (3%)	2 (3%)
Total		30	30	60

The mean restorations EA was 22.6 ± 7 and 45.2 ± 4 degrees, respectively for interproximal and buccal aspects. Mean marginal bone level change (MBL change) was measured by considering different aspects: comparing different timelines, different surgical techniques and different supra-crestal soft tissue heights, respectively.

Mean MBL values were calculated for all the included implants at different follow-up visits: an apical bone remodeling of 0.27, 0.45, 0.47 and 0.56 was calculated at t0 (prosthetic loading), after 1, 2 and 3 years of follow-up (Table 3).

Table 3. Absolute values of MBL in relation to time (T0, T1, T2, T3) without comparison between GD and FH groups.

time	Media	conf.low	conf.high
T0	-0.27	-0.49	-0.05
T1	-0.45	-0.67	-0.23
T2	-0.47	-0.69	-0.25
T3	-0.56	-0.78	-0.35

Also, a statistical comparison was made between MBL in different times (Table 4); no significant differences were found (P values from 0.07 to 0.89). Mean MBL change after 3 years of follow-up in GD and FH groups was 0.35 ± 0.47 and 0.23 ± 0.75 millimeters, respectively (Table 5).

Table 4. Variation of MBL in relation to time (T0, T1, T2, T3) without comparison between GD and FH groups.

contrast	Media	conf.low	conf.high	p.value
T1 - T0	-0.18	-0.39	0.02	0.0783
T2 - T0	-0.20	-0.40	0.01	0.0582
T2 - T1	-0.01	-0.22	0.19	0.8923
T3 - T0	-0.30	-0.50	-0.09	0.0051
T3 - T1	-0.11	-0.32	0.10	0.2908
T3 - T2	-0.10	-0.30	0.11	0.3569

Table 5. Absolute values of MBL in relation to time (T0, T1, T2, T3) and with comparison between GD and FH groups.

FH_GD	time	estimate	conf.low	conf.high
FH	T0	-0.34	-0.57	-0.10
	T1	-0.39	-0.63	-0.16
	T2	-0.48	-0.71	-0.24
	T3	-0.57	-0.81	-0.34
GD	T0	-0.11	-0.48	0.27
	T1	-0.42	-0.80	-0.05
	T2	-0.37	-0.74	0.01
	T3	-0.46	-0.84	-0.09

MBL change difference between the two groups after 3 years of follow-up was 0.11 ± 0.22 mm and such value was not statistically different (p=0.61) as reported in Table 6. Variation of MBL with different STH values in relation to time (t0, t1, t2, t3) was also investigated: for implants with STH less than 3mm a mean MBL of 0.18, 0.46, 0.47 and 0.58mm was measured at t0 (prosthetic loading), after 1, 2 and 3 years of follow-up (Table 7), respectively. Moreover, for implants with STH ≥ 3mm a mean MBL of 0.50, 0.43, 0.44 and 0.51mm was measured at t0 (prosthetic loading), after 1, 2 and 3 years of follow-up (Table 7), respectively.

Table 6. Variation of MBL in relation to time (T0, T1, T2, T3) and with comparison between GD and FH groups.

time	contrast	estimate	conf.low	conf.high	p.value
T0	FH - GD	-0.23	-0.65	0.19	0.29
T1	FH - GD	0.03	-0.39	0.45	0.90
T2	FH - GD	-0.11	-0.53	0.31	0.60
T3	FH - GD	-0.11	-0.53	0.31	0.61

Table 7. Absolute values of MBL with STH values in relation to time (T0, T1, T2, T3).

STH	time	Media	conf.low	conf.high
<3	T0	-0.18	-0.42	0.06
	T1	-0.46	-0.70	-0.22
	T2	-0.47	-0.71	-0.23
	T3	-0.58	-0.82	-0.34
>=3	T0	-0.50	-0.84	-0.17
	T1	-0.43	-0.76	-0.10
	T2	-0.44	-0.78	-0.11
	T3	-0.51	-0.84	-0.18

At time of prosthetic loading the mean MBL for implants with STH less than 3mm was 0.33mm higher than implants with STH ≥ 3mm (Table 8); such value was close to statistically significant (P=0.065). MBL values with STH values related to time (t0, t1, t2, t3) and with comparison between GD and FH groups are reported in Tables 9 and 10, respectively.

Table 8. Variation of MBL with STH values in relation to time (T0, T1, T2, T3).

time	contrast	Media	conf.low	conf.high	p.value
T0	<3 - >=3	0.33	-0.02	0.67	0.065
T1	<3 - >=3	-0.03	-0.38	0.32	0.870
T2	<3 - >=3	-0.03	-0.37	0.32	0.879
T3	<3 - >=3	-0.07	-0.41	0.28	0.710

Table 9. Absolute values of MBL with STH values in relation to time (T0, T1, T2, T3) and with comparison between GD and FH groups.

FH_GD	STH	time	Mean	conf.low	conf.high
FH	<3	T0	-0.17	-0.46	0.12
		T1	-0.33	-0.62	-0.04
		T2	-0.41	-0.71	-0.12
		T3	-0.52	-0.81	-0.23
	>=3	T0	-0.68	-1.08	-0.29
		T1	-0.51	-0.90	-0.11
		T2	-0.58	-0.98	-0.19

FH_GD	STH	time	Mean	conf.low	conf.high
		T3	-0.65	-1.05	-0.26
GD	<3	T0	-0.14	-0.54	0.27
		T1	-0.53	-0.93	-0.12
		T2	-0.47	-0.88	-0.07
		T3	-0.58	-0.98	-0.17
	>=3	T0	-0.06	-0.55	0.43
		T1	-0.11	-0.61	0.38
		T2	-0.05	-0.54	0.44
		T3	-0.12	-0.61	0.37

Table 10. Variation of MBL with STH values in relation to time (T0, T1, T2, T3) and with comparison between GD and FH groups.

FH_GD	time	contrast	estimate	conf.low	conf.high	p.value
FH	T0	<3 - >=3	0.51	0.07	0.96	0.024
	T1	<3 - >=3	0.18	-0.27	0.62	0.430
	T2	<3 - >=3	0.17	-0.28	0.61	0.456
	T3	<3 - >=3	0.13	-0.32	0.58	0.566
GD	T0	<3 - >=3	-0.08	-0.47	0.32	0.702
	T1	<3 - >=3	-0.41	-0.81	-0.02	0.041
	T2	<3 - >=3	-0.42	-0.82	-0.03	0.036
	T3	<3 - >=3	-0.46	-0.86	-0.07	0.022

For the FH group of implants, mean PPD values of 3.7, 3.9, 4.1 and 4.3mm was measured at t0 (prosthetic loading), after 1, 2 and 3 years of follow-up (Table 11). For the GD group of implants, Mean PPD values of 3.6, 3.7, 4.1 and 4.3mm was measured at t0 (prosthetic loading), after 1, 2 and 3 years of follow-up (Table 11). The difference between the two groups at different time was not statistically significant (Table 12).

Table 11. Absolute values of PPD in relation to time (T0, T1, T2, T3) and with comparison between GD and FH groups.

Tecnique	T0	T1	T2	T3
FH	3.763266	3.880916	4.145622	4.322092
GD	3.665771	3.743899	4.118901	4.337650

Table 12. Variation of PPD in relation to time (T0, T1, T2, T3) and with comparison between GD and FH groups.

contrast	time	Estimate	p-value
FH - GD	T0	0.10 (-0.10; 0.29)	0.33
FH - GD	T1	0.14 (-0.06; 0.33)	0.17
FH - GD	T2	0.03 (-0.17; 0.22)	0.79
FH - GD	T3	-0.02 (-0.21; 0.18)	0.88

For the FH group of implants, mBI rate values of 5.7, 18.7, 31.8 and 40.7% was measured at t0 (prosthetic loading), after 1, 2 and 3 years of follow-up (Table 13). For the GD group of implants, mBI rate values of 2.5, 23.3, 34.1 and 47.5% was measured at t0 (prosthetic loading), after 1, 2 and 3 years of follow-up (Table 13). The difference between the two groups at different time was not statistically significant (Table 14).

Table 13 and 14: Rate of mBI in relation to time (T0, T1, T2, T3) and with comparison between GD and FH groups.

Percentages (%)

FH_GD	time	rate	conf.low	conf.high
FH	T0	5.7	2.7	12.1
	T1	18.7	12.2	28.8
	T2	31.8	22.6	44.6
	T3	40.7	30.0	55.4
GD	T0	2.5	0.8	7.9
	T1	23.3	15.2	35.7
	T2	34.1	23.5	49.5
	T3	47.5	34.0	66.3

FH_GD	contrast	ratio	conf.low	conf.high	p.value
FH	T1 / T0	3.29	1.41	7.66	0.0059
	T2 / T0	5.57	2.49	12.46	<0.001
	T3 / T0	7.14	3.24	15.75	<0.001
GD	T1 / T0	9.33	2.84	30.70	<0.001
	T2 / T0	13.67	4.23	44.13	<0.001
	T3 / T0	19.00	5.95	60.67	<0.001

Similar findings were observed for PI indexes. For the FH group of implants, mPI rate values of 11.7, 31.7, 34.2 and 47.5% was measured at t0 (prosthetic loading), after 1, 2 and 3 years of follow-up (Table 13). For the GD group of implants, mBI rate values of 7.2, 35.3, 36.1 and 53.7% was measured at t0 (prosthetic loading), after 1, 2 and 3 years of follow-up (Table 15). The difference between the two groups at different time was not statistically significant (Table 16).

Table 15 and 16: Rate of mPI in relation to time (T0, T1, T2, T3) and with comparison between GD and FH groups.

Percentages (%)

FH_GD	time	rate	conf.low	conf.high
FH	T0	11.7	6.8	20.1
	T1	31.7	22.4	44.8
	T2	34.2	24.4	47.8
	T3	47.5	35.4	63.7
GD	T0	7.2	3.7	14.2
	T1	35.3	24.9	50.0
	T2	36.1	25.5	51.0
	T3	53.7	39.7	72.7

FH_GD	contrast	ratio	conf.low	conf.high	p.value
FH	T1 / T0	2.71	1.47	5.01	0.0014
	T2 / T0	2.93	1.60	5.37	<0.001
	T3 / T0	4.07	2.27	7.31	<0.001
GD	T1 / T0	4.89	2.39	10.01	<0.001
	T2 / T0	5.00	2.44	10.23	<0.001
	T3 / T0	7.44	3.71	14.93	<0.001

In conclusion, no biological and prosthetic complications were observed such as: peri-implant abscess/suppuration/infection, implant mobility, unscrewing/loosening of the restoration, fracture of the prosthetic screw, crown fracture or chipping of the veneering material, loosening between che prosthetic crown and the abutment, fracture of the implant abutment, esthetic impairment, fracture of zirconia framework, fracture of the fixture.

DISCUSSION:

A proper three-dimensional (3D) implant positioning is crucial both for osseointegration and success. Prosthetically-driven placement, infact, is a prerequisite for long term maintenance of implant-supported reconstructions from a biological, esthetic and functional viewpoint (Kadkhodazadeh et al., 2023; Mangano et al., 2015; Mangano et al., 2018; Mangano et al., 2017; Shukri et al., 2023). Incorrect placement of the fixtures within the bone envelope is associated with aesthetic impairment and higher risk of biological and technical/mechanical complications over follow-up (Mangano et al., 2015; Mangano et al., 2017; Mangano et al., 2018). In this RCT, dental implants were positioned by either static computer-guided implant surgery or freehand. Guided implant positioning has progressively gained popularity in the last 20 years as a treatment modality allowing to reach a 3D ideal placement. However, the major part of these studies are based on in vitro (cast models or cadavers) materials. The amount of clinical investigations on fully guided implant placement is limited. In this treatment modality, the entire surgery is digitally planned in advance with a dedicated software in order to obtain an optimal position which aims to reduce biological, esthetic and functional complications of the implant-supported restorations over the years (Colombo et al. 2017; Mouhyi et al. 2019; Nedelcu et al. 2023). Several studies have demonstrated that guided surgery predictably achieve better implant placement when compared to conventional freehand positioning. In this regard, a recent study has been conducted by Cristache et al. aimed at evaluating the precision of dental implant placement by stereolithographic surgical templates. A mean deviation of 0.79 mm (± 0.52) at the entry point, 1.17 mm (± 0.63) at the implant apex, 0.50 mm (± 0.38) apico-coronally and 2.34° (± 0.85) degrees of angular deviation were reported (Cristache et al. 2018). In a similar way, Tan et al. investigated the accuracy of of the final implant position compared to the original digital planning by means of CBCT superimpositions. Interistingly, the authors reported a mean 0.87 mm apical displacement for guided surgery and 1.48 mm apical displacement for conventional freehand positioning. Moreover, the final location of the apex and the angulation of the fixture were significantly closer in case guided surgery had been performed (Tan et al. 2018). According to this, as regards ideal 3D implant positioning, there is a trend showing that fixation of the guides may be helpful as demonstrated

by Pessoa et al. and Kivovics et al. when comparing freehand versus computer guided surgery (Pessoa et al. 2020; Kivovics et al. 2020). In such a scenario, Younes et al. stated that fully guided surgery is the most effective surgical method to place dental implants although it is associated with a higher cost if compared to freehand and partially guided surgery (Younes et al. 2018). Furthermore, entering more deeply into this topic, it is interesting to note that no significant differences were observed by Yimarj et al. in terms of implant location (coronal, apical and angular) between static and dynamic computer-guided surgery (Yimarj et al. 2020). The main outcome of this randomized controlled clinical trial (RCT) was to investigate the marginal bone levels comparing freehand versus fully guided surgery of dental implants designed to be placed 1 mm under the bone crest. It is nowadays unanimously acknowledged that modern implant systems perform better than the older ones. For the latter, indeed, marginal bone loss not exceeding 2 mm after the first year of loading and not exceeding 0.2mm annually in the subsequent 5 years, was deemed as a criteria of success. In this study, the analysis of the results showed that comparing baseline data with those up to 3 years of prosthesis function, no statistically significant differences were observed between freehand and guided surgery. To be more precise, MBL values showed a slight difference at T0 amounting to 0.15 mm (C.I. -0.14; 0.44). On the other hand, after 1 year of loading (T1) a 0.07 mm (C.I. -0.23; 0.36) difference was noticed between the two groups when comparing T0 and T1. Noteworthy, after 3 years of loading (T3), the comparison of MBL values between groups was negative. Indirectly, this finding suggest that a certain amount of bone growth might have occurred in the period comprised between 1 and 3 years of observation. In their systematic review, Carbajal-Mejia et al. investigated the marginal bone loss of implants placed in healed ridges by static computer-guided surgery after at least 1 year of follow-up. The authors reported an average MBL of 1.06 mm (95% CI: 0.83 to 1.30 mm) and 1.48 mm (95% CI: 0.81 to 2.15 mm) after 12 and 36 months of observation, respectively. These results are in agreement with a recent narrative review conducted by Naeini et al. and including 9 systematic reviews with or without meta-analyses (Naeini et al. 2020). In this clinical investigation, dental implants pertaining to the test group (static computer-guided surgery) were placed by nonexperienced operators whereas implants belonging to the control group (freehand conventional implant placement) were placed by experienced operators. As a

consequence of the results obtained in this study, it can be stated that no differences may be observed regarding MBL, irrespective of the operator experience. This assumption can be held true provided that the non experienced operator is assisted by a meticulous digital planning and a precise surgical template. Noteworthy, no statistically significat differences were observed regarding peri-implant related biometric parameters between freehand and guided surgery group. As far as peri-implant probing pocket depth is concerned, quite similar values were obtained at baseline. Infact, PPD amounted to 3.76 mm and 3.67 mm in case of freehand or guided surgery, respectively. The same trend was observed at T_1, T_2 and T_3 as a gradual increase in PPD was noticed. However, after a 3-year follow-up, peri-implant probing pocket depths showed very close values regardless the group they belonged to, measuring on average 4 mm. These PPD values are in line with the current literature in matter of peri-implant health and stability. Indeed, long- term clinical studies have clearly demonstrated that the probing depth of healthy peri- implant mucosa is not always smaller than 4 mm but very often up to 6 mm (Adell et al. 1985; Karoussis et al. 2004). On the basis of the available scientific evidence, the probing depth value cannot be considered per se a reliable indicator to define peri-implantitis (Serino et al. 2008; Serino et al. 2013). In case the real bone loss had not been properly evaluated, for expample due to missing radiograph at baseline, and when PPD was the only used criteria to diagnose and define peri-implantitis, an overestimation of the actual prevalence was observed, as in several previous studies. It seems logical that a progressive worsening of PPD over time, once a physiological steady state in the soft tissue has been established, may be considered as an indicator of an active peri-implant disease. Due to the fact that initial implant location might affect PPD, Huang et al. recommended to record a baseline value in order to provide comparable measurements over time (Huang et al. 2013). In addition, as highlighted by Lee et al. in their recent systematic review, despite using absolute PPD values (e.g. ≥ 4 or 5 mm) it is much more meaningful to understand how it progresses (or worsens) over time. For what concerns plaque and bleeding indices, the dental implants pertaining to this study showed low percentages of both biometric parameters. Such a result may in fact suggest that plaque accumulation and subsequent inflammation might not be related to the positioning technique but rather with the frequency and quality of daily self-performed hygiene and professional

maintenance over the 3-year observation period. Moreover, the authors may address this findings to the careful choice of the prosthetic emergence angle and profiles. Indeed, these parameters were set at the beginning within the prosthetic workflow and employed for crown and bridge manufacturing. A further parameter that was evaluated in this clinical investigation was the supra-crestal soft tissue height (STH) and its potential role as modulator of the peri-implant bone loss and stability, regardless the surgery technique that was used for implant placement. In this regard, it is crucial to highlight that soft tissue thickness and height may play a role on crestal bone changes around dental implants. Indeed, over the past 10 years, an inceasing numbers of studies have reported that initial STH may be associated with marginal bone level change. According to these, if the vertical STH is 2 mm or less, crestal bone resorption amounting approximately to 1.5mm will occur during the formation of a biological seal between the soft tissues and the implant-abutment-restoration surfaces (Vervaeke et al. 2014; Vervaeke et al. 2018; Zukauskas et al. 2021). In this context, vertical soft tissue thickness might be the prerequisite for biological width stability around the implants. This biological seal is the single most important barrier protecting the osseointegrated implant from the contaminated oral environment (Vervaeke et al. 2018). In the present study, less marginal bone loss was observed in relation to the STH variable, irrespective of the original group of assignment of the dental implants. In this scenario, Spinato et al. recently investigated MBL stability in relation to STH values of patients enrolled in the study. On the basis of the vertical mucosal thickness measured after detatching the vestibular flap, implants were placed with the treated part: (group 1) 2 mm below the crestal level in the presence of thin mucosa (<2.5 mm); (group 2) 1 mm below the crestal level in the presence of medium mucosa (2.5-3.5 mm); (group 3) at equicrestal level in the presence of thick mucosa (>3.5 mm). In the presence of thick peri-implant mucosa (height >3.5 mm), very small marginal bone resorption was recorded after 3 months (mean 0.19 mm), which then showed a tendency to become stable after 5 months (mean 0.22 mm). In the event that peri-implant mucosa measured between 2.5 and 3.5 mm, mean marginal bone loss was slightly higher than with thick mucosa, but followed the same trend over time (0.26 mm at T_1 and 0.32 mm at T_2). On the other hand, in the presence of thin peri-implant mucosa (<2.5 mm), significantly higher marginal bone resorption was recorded at different

timepoints (0.41 mm and 0.66 mm at T_1 and T_2, respectively) (Spinato et al. 2022). A further study conducted by Vervaeke et al. investigated the role of STH on peri-implant bone remodeling. In the test group the apico-coronal position of the implant head was adapted in order to leave at least 3 mm of vertical space for biological width establishment. In the control group equicrestal implant placement was performed (Vervaeke et al. 2014). According to this, an implant placed at a site with a mucosal thickness of 2 mm was placed at least 1 mm subcrestally. The authors concluded that anticipating the reestablishment of biological width by adjusting the vertical position of the implant (subcrestal implant placement) seems to be very effective in avoiding the exposure of the implant surface. Similarly, in the present study, differences between STH<3 and STH>=3mm values were calculated with the corresponding 1-year and 3-years follow-ups. Such cut off measure was stated because all the implants were placed 1mm subcrestally, as recommended by the manufacturer. Thus, in the group with STH>=3mm an adequate vertical space for a stable maturation of peri-implant biological width was expected to be provided. On the contrary, for implants with STH<3mm some peri-implant early bone remodeling was supposed to occur. No bias from the prosthetic components were added due to the fixed geometries provided for interproximal and buccal emergence profile shapes and dimensions, as already reported in the inclusion criteria where 3 mm was established to be the cut off measure to divide implants placed set for early peri-implant bone resorption not to occur. In the present study only at baseline (t_0) such kind of clinical trend was confirmed, with a mean difference of 0.33mm of bone remodeling for the group of implants with STH<3mm if compared to that with STH>=3mm. Such a difference is very close to be significant (P=0.06). Because of the relatively reduced sample size of the present trial, the authors suggest to design clinical studies with larger sample size and with STH parameter as primary outcome of the investigations. Finally, regarding the study protocol design, the authors carefully considered the inclusion of two different types of operators: experts and beginners. This decision stemmed from the recognition that assessing the clinical utility of digitally provided templates required comparing the experiences of practitioners with varying skill levels. For expert practitioners, the placement of single implants is routine and does not significantly benefit from digital templates. Therefore, comparing their performance with and without templates would

not yield meaningful insights. Conversely, it is of great interest to explore how digital templates could enhance the practice of less experienced clinicians. However, it is ethically untenable to subject patients to treatment by beginners without adequate support. While acknowledging the ethical constraints, the study underscores the importance of evaluating the efficacy of digital templates in improving outcomes for less experienced practitioners. Furthermore, the authors acknowledge the limitation of the sample size in terms of the number of patients and implants. Future research should consider recruiting a larger and more diverse sample of patients and implants to assess the validity of the present findings.

CONCLUSIONS:

- No statistically significant differences were found between freehand and static computer-guided implant placement regarding marginal bone levels over 3 years of observation.
- Provided that implant-supported rehabilitations be designed with correct emergence angles and profiles, subcrestal implant positioning not exceeding 1 mm of dental implants featured by precise and tight connection might result in more than acceptable peri-implant related biometric parameters after 3 years
- Soft tissue height >3mm at the time of implant placement may reduce bone remodeling and exposure of the coronal portion of the implant. It seems that, in case of STH <3mm, a more apical positioning of the implant head would be preferable.

Implant positioning through static computer-guided surgery performed by a non-experienced operator does not prevent or reduce marginal bone remodeling itself when compared to freehand implant placement performed by an experienced operator. However, digital planning and guided surgery may help non-experienced operators perform implant placement with a similar accuracy if compared to expert ones. Marginal bone levels seem to be influenced by the amount of soft tissue height in a sub-crestally placed implants with an internal conical connection and platform switching of the abutment diameter. Nevertheless, such radiological trend is significant only in the early phase of peri- implant hard and soft tissue establishment.

Further studies featured by medium- (5 years) and long-term (10 years) follow-up are warranted.

FINAL REMARKS:

The present thesis investigated, through different study designs, the role of some of the most important factors that may affect MBL around dental implants specifically designed to be placed subcrestally. It should be noticed that such biomedical devices have become widely used in everyday clinical implant practice only in the last 10 years. According to this, the clinical validation of such implants is currently under study and, to date, there are very few clinical studies in the literature concerning subcrestal implants. The first publication covered by this thesis is a retrospective study published in 2020 (Study I.). The rationale behind such a retrospective investigation was based on the fact that the vast majority of articles in the literature, up to that moment, had reported follow-ups which were almost never longer than 18 months. The most important features of this study are certainly the duration of follow-up (mean 2.72 ± 1.31 years, ranging from 2 to 9 years) and the sample size, which still represents one of the studies with the largest number of investigated subcrestal implants. It is also interesting to notice that the average MBLchange observed was only 0.09 mm, between the baseline and the last follow-up visit. Furthermore, the mean MBL value at the last follow-up visit was −1.00 ± 0.37 mm. The negative value indicated a more coronal bone level than the outermost edge of the implant neck, namely the starting point from which the measurements were taken. This value is extremely relevant considering that Windael et al. in a recently published 10-year prospective study showed a threshold value of 0.5mm above which early marginal bone loss increases the odds ratio of developing peri-implantitis by a factor of 5.43. One might speculate that subcrestal implant placement may limit the initial MBL and consequently, by never exposing the rough implant surface to the oral environment, also the MBL in the medium to long term. Nevertheless, it is not possible to make such a statement due to the nature of the study design. A retrospective study may in fact allow to investigate possible factors associated with a specific variable under study. It should be emphasized that such data should be derived from interventional studies of appropriate methodology characterized by follow-ups longer than 5-10 years. After applying a multiple linear regression model, it was indeed found that the greatest predictor of bone loss was the total time of function (i.e. follow-up) of the implant-supported prostheses. Further predictors of MBLchange were the vertical position of the IAI in relation to the bone

crest at the time of placement and type 2 diabetes (controlled), respectively. In order to investigate the prosthetic factors that may play a role in determining early marginal bone loss, a review of the literature on the prosthetic emergence angle (EA) was conducted (Study IV.). After performing the screening phase and full-text analyses, 5 studies were included. Although the inclusion criteria were broad enough to allow as many clinical studies as possible to be identified (i.e. clinical studies published in English language with at least 10 patients) only few articles fulfilled the inclusion criteria. Specifically, two studies (Katafuchi et al. 2018 & Yi et al.2020) concluded that interproximal EA > 30° could be considered as a risk factor for the development of peri-implantitis. Nevertheless, the major part of the data reported by these studies refers to old-fashioned implants featuring external connections without platform-switching. In this regard, a systematic review and meta-analysis recently published by Atieh et al. concluded that a prosthetic emergence angle greater or less than 30 degrees may not, per se, play such a crucial role in determining MBL. The authors suggest that additional factors such as the precision of the implant-abutment connection, microgap reduction, and the presence of platform-switching may have a greater role in this regard, although the quality of the scientific evidence supporting this affirmation is still low to moderate (Atieh et al. 2023). Two retrospective investigations were then conducted with the aim to assess the role of EA in subcrestally placed implants (Study II. & III.). Both studies were published in 2022 and evaluated subcrestal implants at 3-year follow-up. Firstly, the role of the interproximal prosthetic emergence angle was investigated (Study II.). The emergence angle was defined as the angle of intersection between a first line running parallel to the long axis of the implant and a second one which was drawn tangential to the most external contour of the restoration starting from the IAI, on standardized radiographs. Three hundred twelve implants positioned in 74 patients were analyzed. Noteworthy, no statistically significant difference in terms of MBLchange, modified sulcus bleeding index and plaque index were observed when emergence angles greater than 30 degrees were compared to emergence angles less than 30 degrees. Both groups showed MBLchange of just 0.06 mm which represent a more than acceptable radiographic bone loss. Moreover, such amount of MBLchange is far lower than the threshold value of 0.5 mm proposed by Windael. The Study III. was conducted to investigate the role of buccal EA in the aesthetic area, meaning the zone

comprised between and including premolars. To the best of our knowledge, it is the only study in literature to date having investigated the buccal EA on peri-implant related biometric parameters. In fact, radiographic assessments of the vestibular bone can only be made by comparing three-dimensional radiographic examinations (i.e. CBCT) over time since intraoral x-rays allow to evaluate MBL at the mesial and distal aspects. Due to ethical reasons, it can be deduced that this is not feasible. The buccal emergence angle was calculated digitally by turning the physical plaster models into digital ones by means of a scanning procedure. The most important findings of this study were the absence of statistical significance regarding probing pocket depth, plaque index and bleeding index. The mean PPD calculated for buccal EA>30° amounted to 1.86 while the same value calulated for EA<30° was 1.81 mm with a mean PPD difference of 0.062 mm. It has to be highlighted that both interproximal and buccal emergence angles in study II. and III. never exceeded 50 degrees. According to the study II. and III. it is suggested that emergence angles comprised between 30 and 50 degrees may not impair the clinical and radiographical outcomes of subcrestally placed implants up to 3 years. Due to the retrospective design of the studies, these finding should be interpreted cautiously. Diverse surgical factors potentially affecting MBL in subcrestally placed implants were finally investigated by a parallel-arm randomized controlled clinical trial (Study V.). Patients were recruited, treated and followed-up in the period comprised between 2018 and 2023. Sixty implants (30 per group) in 18 patients were analyzed at the time of prosthetic loading (T0) and each year thereafter up to 3 years (i.e. T1, T2 and T3). The primary outcome was to compare implant placement via static computer guided surgery performed by an inexperienced operator (test group) versus implant placement perfomed freehand by an expert surgeon (control group). The mean MBL change between the groups after 3 years was 0.11 mm ± 0.22 mm which was not statistically significant. In contrast to previous studies, no harmful effect of static guided surgery on marginal bone loss was observed in the present investigation. It can be assumed that the cutting efficiency of the drill sequence along with an adequate cooling system may impede overheating at the surgical site during implant bed preparation. Nevertheless, it should be emphasized that biological overheating damage has the greatest impact in the very early phases of healing and could be detected radiographically before the prosthetic loading. Moreover, data suggest that MBL may not

be affected by the experience of the surgeon in single implant placement. In fact, it is interesting to notice that inexperienced operators using surgical templates, provided that proper planning has been carried out in advance, may achieve similar outcomes than experienced operator placing implants freehand. To conclude, even in the absence of statistical significance, STH <3 mm showed increased bone loss (0.33mm) when compared to STH>3mm, irrespective of the allocation group.

According to the above-mentioned clinical studies, the present thesis succeeded in identifying the clinical validation of subcrestally placed implants in the short-medium term follow-up. Due to the lack of long-term clinical data (i.e. 10 years), further studies characterized by adequate methology and longer follow-up are strongly advocated.

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